DIFFUSE LARGE B CELL LYMPHOMA - CLINICAL PROGNOSTIC FACTORS
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Introduction: Although the survival of patients (pts) with diffuse large B cell lymphoma (DLBCL) has improved considerably, many pts still die with progressive disease. Over the last years, efforts have been made in an attempt to identify at diagnosis the features (prognostic factors) that could help predict which pts will progress after conventional chemotherapy.

Methods: Adult pts with DLBCL, admitted to IPO - Porto between Jan.90 and July98 were retrospectively evaluated for clinical features predictive of overall survival (OS) and disease-free survival (DFS). All the pathologic results were revised by the same pathologist. The prognostic value of the International Prognostic Index (IPI) was also evaluated.

Results: From the 116 pts admitted, 9 were excluded. The predicted 5-year OS and DFS rate for the 95 pts treated with anthracycline based schemes was 54% and 39% respectively. Percent survival (PS), B symptoms, Ann Arbor stage, number of extranodal areas involved, LDH, lymphopenia (<1000/uL), hypoproteinemia (<60 g/l) and/or hipoalbuminemia (<35 g/l), and B2-M, significantly influenced the OS and DFS (p<0.05). Patient’s age (≤ 60 yr or > 60 years old) significantly influenced the OS (p=0.04) and the presence of a tumor mass ≥ 10 cm reduced survival (p=0.02). Sex, nodal extrasanodal location, bone marrow or liver involvement, high ESR, and the time elapsed from the first symptom to diagnosis had no prognostic value. In respect to IPI, the 5-year OS and DFS rates were respectively 73% and 80% for low IPI pts (0-1 risk factors), 37% and 47% for pts with intermediate IPI, 8% and 19% for high intermediate IPI pts and 0% for pts with high IPI (≥ 5 risk factors). In a multivariate analysis 3 features were independently associated with OS: IPI (p=0.002), hypoproteinemia (p=0.033) and the chemotherapy scheme (p=0.027).

Conclusions: IPI, the presence or absence of hypoproteinemia, and the chemotherapy scheme can be considered prognostic factors. The presence of B symptoms, lymphopenia, hipoalbuminemia and B2-M had a negative impact on the outcome (OS and DFS).

8. Aggressive Lymphomas

BLASTOID AND COMMON VARIANT OF MANTLE CELL LYMPHOMA: MORPHOLOGICAL, MOLECULAR, AND CLINICAL COMPARATIVE STUDY.
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Introduction: According to the WHO classification, blastoid variants of mantle cell lymphoma (MCL) are considered to be of more aggressive potential. Their identification only relies on morphological criteria. The aim of our study was to determine whether molecular or genetic features may support the diagnosis of MCL blastoid variant on routine specimens.

Methods: Since 1997, 19 patients with MCL were recorded and followed at our institution. All cases exhibited a CDS+, CD20+, CD23+ phenotype. A t(11;14) fusion signal was detected by interphase FISH in all tested cases (100%).

Results: Fifteen cases were common MCL and four cases (21%) were blastoid variant arising either de novo (n=3) or at relapse (n=1). No clinical or biological difference was observed between blastoid and common MCL at presentation. Overall duration of response after first line therapy (1 to 28 months) and overall survival (20 versus 42 months) appeared shorter in blastoid variant than in common type. Only the four blastoid cases were characterized by a CCND1 gene amplification detected by interphase FISH at the level of (11;14) nuclei. This amplification was associated with a higher percentage of CyclinD1 positive cells (n=2) and a proliferation index above 600 for part of the cases.

Conclusion: Beside morphology, interphase FISH showed that only blastoid MCL variants were characterized by CCND1 gene amplification. Whether this lead to a higher overexpression of cyclin D1 transcripts in blastoid cases than in classical MCL is currently under investigation. These biological features could be relevant for the diagnosis of aggressive variants of MCL.

Title – THE STUDY OF PROLIFERATIVE INDEX AS A PROGNOSTIC INDICATOR IN INTERMEDIATE AND HIGH GRADE NON HODGKIN'S LYMPHOMA USING MB1.
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Introduction: The existing prognostic index for intermediate and high grade NHL does not identify a subgroup of patients for whom the currently available therapy (CHOP) is inadequate. With a view to identify these subgroups of patients, a study was undertaken using proliferative index as prognostic indicator.

Methods: Thirty-seven patients with intermediate and high grade NHL were included in the study. All patients underwent staging investigations and had histologically proven intermediate or high grade NHL. MIB1 was quantified by determining the positive cells expressing the nuclear MIB1 using a monoclonal mouse antibody (Clone MIB1). The proliferating index (PI) was then calculated in each patient by identifying all the cells with positive MIB1 staining (as distinct from the background staining of the normal cells). The PI was calculated using an image analyser. The proliferative index was determined for the entire tumour mass.

Results: Five patients (14%) had a PI > 10, five patients had a PI between 5 to 10 and 27 patients had a PI < 5. There was a significant correlation between the PI and the duration of survival of the patients (p<0.01).

Conclusion: The proliferative index can be used as a prognostic indicator in NHL. A PI > 10 is associated with a shorter survival as compared to patients with a PI between 5 to 10 and < 5.

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Cell kinetic data are important indicator of the aggressiveness of tumour and clinical response. The ki-67 antigen plays a pivotal role in role in maintaining cell proliferation and the expression of this antigen was found to be a valuable indicator for aggressive disease in a variety of neoplastic disorders. This study aimed to assess the prognostic significance of expression of ki-67 antigen in peripheral lymphoid tissue and bone marrow, using the monoclonal antibody MIB1 that is applicable in formalin-fixed paraffin embedded samples in cases with high-grade non-Hodgkin's lymphoma.

The MIB1 immunostaining was performed on 96 samples from 48 patients with high-grade lymphomas. The study was performed on tissue sections, nodal or extranodal, as described in detail. The Ki-67 index was determined using an image analyser. Forty-five out of the studied 48 cases (93.8%) were positive with a median labelling index of 20.42% (Range 0.58). We were able to detect minimal residual disease in BM by detecting MIB1-positive cells in BM samples of 29 patients who were not morphologically diagnosed to have BM infiltration.

There was a strong correlation between BM positivity for ki-67 and ki-67 labelling index (p < 0.01). Twenty-eight patients (58.3%) achieved complete remission (CR). The median duration of CR was 35 months (range, 8 - 98 months), and the overall survival at 48 months was 35.4% (median, 22 months, 95% CI, 13.1-31.1 months). Their median ki-67 index (20.42%) was chosen as a cut-off level for statistical analysis of the variables that influence clinical outcome. Using univariate analysis, high MIB1 -1 labelling index (≥ 20.42%) was associated with shorter duration of complete remission (p=0.01). Multivariate analysis showed that an extended overall survival time was associated with low MIB1-1 labelling index (< 20.42%) and with the known clinical variables included within the International Prognostic Index (PI). None of the patients with high intermediate or high PI who expressed high Ki-67 labelling index showed a long term survival as compared to the group of patients with low intermediate PI and low Ki-67 labelling index (p=0.001). Minimal residual disease in BM as detected by MIB1 was correlated in univariate analysis (p=0.04), although not confirmed in multivariate analysis, with poor survival.

In conclusion, the M1-1 monoclonal antibody immunostaining appears to be a simple and reproducible method of determining tumour proliferative index and provides useful prognostic information in patients with high - grade NHL. It can further define the poor risk subgroup in the low and intermediate PI groups and the good risk subgroup in the high intermediate and high risk IPI groups.
IMMUNOHISTOCHEMICAL EXPRESSION OF CD40 MAY PROVIDE PROGNOSTIC INFORMATION IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: In search for subgroups of diffuse large B-cell lymphoma (DLBCL) with different histogenetic origin and prognosis (as has been described by gene expression profiling), we examined tumor specimens from 125 patients with DLBCL, uniformly treated by either CHOP or MACOP-B in a multi-center trial set by the Nordic Lymphoma Group 1989-1994.

Methods: Bcl-6, CD10 and CD40 were chosen as markers for a germinal centre phenotype and CD138 as a marker for post-germinal centre origin.

For histopathological review, the following markers were analysed on formalin-fixed/paraffin embedded tissues employing the EnVision® method:

CD5, CD20, CD21, CD22, CD23, CD75, CD79a and cyclin D1.

The results were compared to outcome regarding time to treatment failure (TTF) and overall survival (OS).

Results: CD10 was positive in 51% and bcl-6 in 97% of the cases. No prognostic conclusions could be drawn from analysis of these factors. CD40 was positive in 66% of the cases. This group was associated with superior TTF (p=0.027) and OS (p=0.0068) by Cox regression analysis, positivity for CD40 was shown to be a prognostic factor for OS, independent of IPI.

No conclusions could be drawn from analysis of CD138 since only a minority were positive.

Conclusion: In DLBCL, tumor expression of CD40 was associated with prolonged TTF and OS. The biological background for CD40-positive in DLBCL, in complex, CD40 is essential for germinal centre formation, and its expression may correlate with a germinal centre origin, but could also represent a functional subgroup with other properties regarding T-cell interaction and autologous tumor response. Confirmatory studies will be necessary.

PRETREATMENT PROGNOSTIC RELEVANCE OF BCL-6, CASPASE 3, PARP, VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) EXPRESSION AND INTERNATIONAL INDEX IN DIFFUSE LARGE B CELL LYMPHOMA

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Introduction: Diffuse large B cell lymphomas (DLBCL) represent a heterogeneous entity that includes centroblastic (CB), immunoblastic (IB) and B-cell large cell anaplastic (Ki1+)-lymphomas. DLBCL have been associated with some molecular lesions, but the role of such lesions as prognostic markers is still controversial. Survival can be predicted on the basis of pretreatment clinical characteristics established as the IPI. The aim of our study was to confirm prognostic relevance of highly heterogeneous DLBCL from both a clinical and histopathological point of view.

Methods: We analyzed 65 pts with de novo DLBCL categorized clinically by IPI. All biopsy specimens were diagnosed by the histomorphology (REAL and updated Ki67 classification) and by immunohistochemistry. The paraffin embedded samples were further analyzed for the expression pattern of bcl-6 protein, Caspase-3, PARP and protein for VEGF. All results were statistically confirmed by analysis of nonparametric parameters.

Results: Pathohistological analyses showed 55 pts with CB and 10 pts with IB DLBCL. The IPI was low in 26.9%, low intermediates in 29.2%, high intermediates in 27.6% and high in 15.1%. CB pts had high intermediate and high IPI. During the 48 months follow-up period, 38/65 pts (58.4%) were alive and under control (ten IPI pts died). All analyzed samples were bcl-6+, but in 48 centroblastic pts we noticed statistical significant strong positivity (>75% cells), p=0.04. The similar results were obtained for Caspase-3. PARP was strongly positive in 45 pt, mainly of centroblastic type. There were no statistical significant difference between CB and IB in VEGF expression but we observed 10 completely negative reaction in CB pts only.

Conclusion: IPI was statistically significant higher in IB pts. Contrary, bcl-6 and Caspase-3 were statistically significantly higher in CB pts; PARP was strongly positive in CB and VEGF expression was mainly negative. IPI as clinical marker together with bcl-6 and caspase-3 can be used to differentiate CB and IB DLBLC, and can serve as the valid prognostic markers in DLBCL.

CLINICAL SIGNIFICANCE OF BCL-2, BCL-6 AND CD-10 EXPRESSION IN DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous group with respect to clinical, histopathological and evolutive prognostic set of criteria to design therapy. However, IPI does not consider the biological potential of tumor cells. The aim of our study was to determine whether routine phenotypic features, besides IPI, may influence survival.

Methods: Seventy-six patients were recorded and their characteristics were: median age, 57 years (16 to 84); stage III-IV, 65%; LDH greater than 1N, 58%; performance status more than 1, 24%; extranodal sites more than 1, 14%; IPI above 2, 42%; 75 patients received anthracyclin-based combination chemotherapy followed by involved-field radiotherapy (n=21) and/or autologous stem cell transplantation (n=24). We studied bcl-2, bcl-6 (DAKO) and CD-10 (Novocastan) immunoreactivity on formalin-fixed sections.

Survival curves were estimated by the Kaplan-Meier method and compared by the log-rank test.

Results: Overall survival (OS) was 51.6% with a median follow-up of 23 months. Bcl-2, bcl-6 and CD-10 expression were observed in 48 (63%), 53 (76%), 22 (29%) patients, respectively. OS was influenced by IPI (p=0.00011) but not by bcl-2 (p=0,11), bcl-6 (p=0,51) or extranodal sites (p=0,63) expression. Bcl-2 negative cases were significantly associated with higher event-free survival (EFS) (89% vs 49%, p=0,02), especially in association with bcl6 expression (p=0,04).

Conclusions: The expression of bcl-2, bcl-6 and CD-10 did not influence OS. A Bcl-2+ phenotype was associated with a worse event-free survival while a bcl-2/bcl6+ phenotype seems to define a favourable subgroup.

CLINICAL SIGNIFICANCE OF BCL-2, P53 AND KI67 PROTEIN EXPRESSION IN DIFFUSE LARGE B-CELL LYMPHOMA


Patients and Methods: during the last three years we studied all consecutive patients with DLBCL at diagnosis. Only patients with too small biopsy sample were excluded. Protein expression was analyzed on paraffin-embedded tumor tissue by immunohistochemistry in relation to clinical factors: stage, age, percentage of neoplastic cells and percent positive. Comparisons were made by χ². Survival curves were constructed by the Kaplan-Meier method and compared by the log-rank test.

Results: seventy-one patients were studied. Thirty-eight (53%) were females and 39 (56%) were older than 60 y. Clinical presentation was: stage III-IV 40/66 (61%), B-symptoms 19/69 (27%), bulky disease 32/67 (48%), extranodal disease 56/69 (83%); ECOG 2 3 14/68 (50%), high LDH 59/65 (60%), IPI 2 4 66/65 (71%). Forty-three (61%) expressed bcl-2, 14/63 (22%) expressed p53 and all cases had a strong expression of Ki67. Bcl-2 expression was not associated to differences in clinical presentation. Patients with bulky disease expressed p53 less frequently (8% vs 93%, p=0.03). Overall, 62/67 (93%) patients received treatment (93% chemotherapy, 87% with CHOP or CHOP-like regimens). 39/51 (76%) responded to therapy. Patients with p53 expression responded worse to therapy (CR+PR: 14% vs 85%, p=0.07).

With a median follow-up of 7.2 mo, overall survival (OS) of the whole group was 54%, with a plateau after 12 mo, and the median event-free survival (EFS) was 6.8 mo. EFS was significantly worse in patients with p53 expression (p=0.05), but there was no significant differences in OS.

Conclusion: patients with DLBCL and p53 protein expression respond worse to therapy and have a significantly worse EFS.
MULTI-COLOUR FISH ANALYSIS OF DIFFUSE LARGE B CELL LYMPHOMA: COMPARISON WITH CONVENTIONAL CYTOGENETICS
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Conventional cytogenetic (CC) analysis and interphase FISH analysis using specific DNA probes has resulted in the identification of non-random chromosomal abnormalities in DLBCL. However, comprehensive analysis is often difficult due to technical difficulties in obtaining high quality metaphase cells from solid tumour samples, and the complexity of the tumour genome. M-FISH is a recently developed technique by which each of the human chromosomes can be labelled with unique combinations of fluorochromes. In metaphase preparations that are suboptimal for G-banding the application of M-FISH is possible allowing the analysis of both structural and numerical aberrations in a single experiment.

Fresh lymph node biopsies were received and cells were disaggregated into culture medium. Cells were harvested and G-banding carried out using standard cytogenetic protocols. Metaphase cells were obtained in 9 cases (6 presentation and 3 relapse cases) of DLBCL and slides were prepared for M-FISH using the 24Xcyte kit (MetaSystems, GmbH). Images were captured and analysed using a Zeiss AxiosPlan imaging microscope and ISIS32 software (MetaSystems, GmbH).

This study using M-FISH has shown that almost all DLBCL cases have multiple numerical and structural abnormalities. 1/3 cases which had a normal G-banding result was found to have I(11)(q14) by M-FISH. 9/9 abnormal cases were abnormal using M-FISH, with 8/9 having structural abnormalities. 1/3 cases with +7, +7 and +18 by G-banding had I(11)(q14) detected by M-FISH. ‘Marker’ chromosomes that could not be further evaluated by G-banding were identified in all cases by M-FISH. These usually consisted of unbalanced translocations frequently involving chromosomes 1, 3, 7, 11, 12, 14 and 18 and appeared to be random. The sensitivity of M-FISH was poor for assigning breakpoints, continuing the need for techniques such as PCR and interphase FISH. However, global screening of cases with poor chromosome morphology and complex karyotypes is possible with M-FISH, which is an improvement on conventional cytogenetics. The identification of novel structural rearrangements may add prognostic information in DLBCL.

IMMUNOREACTIVITY FOR CD56 BUT NOT FOR CD4 AND CD3 STRATEGIES DIFFERENT RISK GROUPS IN STAGE III DIFFUSE LARGE B-CELL LYMPHOMAS (DLCL) OF THE ANN ARBOR STAGE III

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Background: Two molecularly and prognostically distinct profiles of DLCL, defined ‘germinal center-like’ and ‘activated-like’ DLCL have been defined. Three immunohistochemical B-cell ‘germinal center-like’ signature markers, bo4, CD10 and CD38, could be helpful for distinguishing the two types of DLCL, whose prognostic implications in stage III-IIA primary gastric B-cell lymphomas (PGCL) have not been assessed thus far. Purpose: To analyze the immunoreactivity (IR) and prognostic implications of bo4, CD10 and CD38 in PGCL. Methods: Clinical and pathological data of 103 gastric lymphomas were reviewed. Histopathology were low-grade marginal zone lymphomas of MALT-type (MALT, n=41) and diffuse large B-cell lymphoma with (DLCLM, n=31) or without (DLCL, n=31) areas of DLCL. IR was studied with the ABC method. LGC cases were analyzed separately from larger cell lymphomas (DLCLM + DLCL). The prognostic value of the three markers was analyzed both as continuous variable and using the mean value of IR (percentage of positive cells/neoplastic cells) as cut-off. Results: bo4 was positive in 7 LGC cases (17%), 132 DLCL (57%), and 15 DLCL (6%) (p<0.002), with a mean of 4, 28 and 34% immunoreactive neoplastic cells, respectively. CD10 was positive in 4 DLCLM (17%) and 9 DLCL (29%) (p=0.0002), with a mean of 13 and 24% immunoreactive neoplastic cells, respectively. No cases of LGC were reactive for CD10. CD38 was positive in 12 LGC (30%), 6 DLCLM (3%) and 9 DLCL (30%) (p<0.002), with a mean of 27, 21 and 25% respectively, broadly correlated with progression overall survival (OS) either in the whole series or in the LGC subgroup. With the exception of CD10, which was associated with a significant inferior OS in DLCLM (54.3 vs. 75.4 months, p=0.05), the lack of statistical significance in OS comparison was related to the low frequency of expression. In the LGC series, CD10 was the only marker which showed a significant correlation with OS, OS (27 vs. 72 months, p=0.05), and, among LGC, CD10+ cases showed a significant shorter progression free survival (PFS). The lack of correlation between CD38 expression and OS could be related to the high expression of IgD in many cases, that could be responsible for the heterogeneous expression of CD38. An interesting correlation was observed between PFS and CD10 expression in DLCL, long PFS (≥9 months) being associated to CD10 negative cases. The expression of CD10 in LGC was significantly correlated with both clinical stage and primary treatment, with CD10 positive cases showing a significantly higher OS, as compared to CD10 negative cases. The expression of bo4 was associated with both histopathology and clinical stage, with bo4 positive cases showing a significantly higher OS, as compared to bo4 negative cases.

EXPRESSION OF APOPTOSIS-RELATED PROTEINS IN DIFFUSE LARGE B-CELL LYMPHOMAS

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Introduction. Diffuse large B-cell lymphomas (DLBCL) represent a biologically and clinically heterogeneous group. Though, these tumors are curable with chemotherapy, their response to treatment varies. Apoptosis-related proteins play an important role in the chemosensitivity or chemoresistance of tumors. The aim of this study was to investigate the expression of apoptosis-regulating proteins in DLBCL cells to indicate of tumor chemosensitivity.

Methods. The expression of bcl-2, mcl-1, bak, bax, and p53 proteins was examined on paraffin sections from 45 cases of DLBCL (30 centrolobular, 3 immunoblastic, 2 Burkitt-like, 2 anaplastic, 1 T-cell/BCL, 1 primary nodal) using monoclonal and polyclonal antibodies, and the labelled streptavidin biotin technique. Specimens containing >10% immunostained tumor cells were considered positive. Clinical data were available for 31 cases (19 chemosensitive, 12 chemoresistant).

Results. Bcl-2, mcl-1, bak, bax and p53 positive immunostaining was detected in 64.4%, 84.4%, 100%, 80% and 80% of cases, respectively. Bcl-2 family proteins (bcl-2, mcl-1, bak, bax) were overexpressed in most cases. A higher expression of bcl-2 (75% vs 57.9%), mcl-1 (100% vs 78.9%), bax (83.3% vs 63.2%) and p53 (91.7% vs 73.7%) was observed in chemoresistant cases. A significant association was found between the expression of bcl-2 and mcl-1 in the group of chemoresistant tumors (p=0.008).

Conclusion. Bcl-2, mcl-1, bak, bax and p53 proteins are overexpressed in DLBCL. These proteins are expressed more frequently in chemoresistant lymphomas.

D NA REPAIR ABNORMALITIES LEADING TO RADIATION SENSITIVITY IN MANTLE CELL LYMPHOMA

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Mantle cell lymphomas (MCL) are characterized by their aggressive behavior and poor response to chemotherapy regimens. Recently, the ATM protein, involved in DNA damage control after irradiation has been shown to be inactivated in MCL. ATM deficiency could be a major abnormality in the lymphoma genetics but could also increase the radiosensitivity of MCL cells. To test this hypothesis, we have used two cell lines generated from two patients with MCL at terminal phase of their disease: one with 75% of wild-type (WT) ATM and the other with 5% of ATM, which had typical MCL with cyclin D1 hyper-expression. A masked cell line (11;14) (UPFN1) or a typical (11;14) (UPFN2). In addition the UPFN2 cells contained numerous cytogenetic aberrations. The normal cells observed in the cell lines were identical to those found in the fresh MCL cells. To determine the radiosensitivity, clonogenic survival assays as well as FISH assays were used before and after irradiation at 2 Gy and 4 Gy. Apoptotic cell death was evaluated by TUNEL assays. Both UPFN1 and UPFN2 cells were highly sensitive to irradiation (Survival fraction at 2 Gy (SF24h): 24% and 7% respectively). The frequency of chromosomal aberrations induced by irradiation was higher in UPFN1 cells as compared to UPFN2 cells. However, despite their increased radiosensitivity, UPFN2 cells were totally resistant to apoptotic cell death whereas UPFN1 cells underwent apoptotic cell death 4 days after irradiation. To study the molecular bases of this differential behavior, ultradeep sequencing of Southern blot was performed in both MCL cell lines. Fluorescence-assisted Microarray Analysis (FAMA) was chosen to detect ATM mutation. In UPFN2 a deletion of one ATM allele and a point mutation in the remaining allele was detected in Fas3 kinase domain. However, in UPFN2 a biallelic ATM without mutation was found. We have evaluated Western blots the levels of Ku70 protein, involved in DNA repair. In UPFN1, Ku70 levels were identical to control and they decreased 1 and 24 hours after irradiation as expected. In contrast, UPFN2 cells had very low baseline levels of Ku70 which were not increased after irradiation. Similarly, their cell line showed an ATM type (wp53 protein resulting in ATM mutation. In the UPFN1, wp53 expressed was similar to that seen in control cells. Thus, these results demonstrate that MCL cells show an increased radiosensitivity, which can be the result of distinct molecular events, such as a novel ATM gene at the 14q32 locus. Finally, the radiosensitivity of MCL cells could clinically be exploited to increase the minimal response rates of MCL patients to the current chemotherapy regimens.
HIGH-DOSE CYCLOPHOSPHAMIDE (CTX) IN CHOP REGIMEN IS SAFE, not TREATMENT-RELATED MORTALITY IN PATIENTS WITH AGGRESSIVE NON-HODGKIN LYMPHOMA, AND DO NOT IMPAIR FERTILITY OF FEMALE PATIENTS. EJ. Debnath,
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CHOP is considered standard therapy for patients with aggressive non-Hodgkin lymphoma. However, no evidence of its safety has been reported. The toxicity and efficacy are difficult to interpret due to the multiple changes in the regimen. A prospective study was initiated in a single center evaluating escalating doses of CTX only in patients with aggressive lymphoma. Eligibility criteria were: performance status 0-2; stage I/II bulky or stage III, IV with an IPI of ≥ 2 points; age ≥ 60 years. Between 2006 and 2008, 69 patients were enrolled: 25 female, 21 male with a median age 42 yr, (range 31-64 yr). The dose was administered CTX in a 4-week cycle 2 cycles in 3 cycles. The Response rate to CTX was 80% in patients who received at least 3 cycles of CTX. In conclusion, high-dose CTX is feasible and effective in patients with CHOP. Further studies are required to evaluate the long-term outcomes of patients treated with high-dose CTX.
SIGNIFICANT DOSE ESCALATION OF IDARUBICIN IN THE TREATMENT OF AGGRESSIVE NON-HODGKIN'S LYMPHOMA LEADS TO INCREASED HEMATOPOIETIC TOXICITY WITHOUT IMPROVEMENT OF EFFICACY: FINAL RESULTS OF A PHASE III TRIAL OF THE GERMAN HIGH GRADING NHL STUDY GROUP (DSHNHL)


Objective: A Phase III dose escalation study substituting Id for D in the CHOP-IE regimen in order to determine the Id dose with equal hematopoietic toxicity compared to D (maximum practical dose) in a 14-day regimen was performed. Background: CHOP in 14-day intervals and CHOEP improve treatment results significantly (PFandrich et al., Blood 98, 2001). Idarubicin (Id) is an anthracine with proven activity against lymphoma and prolonged pharmacokinetic properties compared to doxorubicin (D). Results of an Italian study (Zinzani et al., 1996) comparing CHOEP with CHOP showed equivalent efficacy and lower toxicity for the CHOEP arm at a dose of 10 mg Id. Patients and Methods: Patients (pts; PS 0-3, BM inv. ≤ 25%, normal WBC/platelets, no significant major organ dysfunction; age 18-75 y) with aggressive NHL, received 6 cycles of CIVEP-14. CIVEP-14 consisted of Id (1.16 mg/m² d1), dexamethasone (750 mg/m² d1), vincristine (2 mg/m² d1), etoposide (100 mg/m² d1-3) and prednisone (100 mg/m² d1-3) - G-CSF (d5-13). Results: Between 11/96 and 09/98, 64 pts from 7 centres included, 9 pts had to be formally excluded at the final evaluation. 55 pts, median age 56 (range 23-71) m, 27 f, were evaluated with a median observation time of 40 mos. 78% of pts had IPI scores 0/1, 13% IPI 2, 4% IPI 3 and 5% IPI 4/5. 22% had bulky disease (N2/m2), and 54.6% extranodal disease. Id dose could be escalated to a max. of 16 mg/m² (24 pts). Treatment had to be terminated earlier than planned in 8/55 pts due to toxicity. The CR-rate was 77.4% (95%-CI 66-87,8%) the TTF-rates were 59,1% resp. 51,7% at 2 resp. 3 yrs. and the OS was 71.3% resp. 63.6% in 13/55 pts have died due to lymphoma PRO, and 2/55 pts due to treatment related toxicity. Compared to CHOP-IE, cumulative hematotoxicity was increased with subsequent reductions in planned dose intensities, even at low 14 levels. Conclusion: The Id/D dose equivalence is 1.5 to 5 rather than 1 to 5 as in the CHOEP-14 regimen. Id was therefore underdosed in previous trials. The Id dose increase does not translate into higher efficacy but increases hematotoxicity. Doxorubicin remains the standard anthracine for the treatment of aggressive NHL.

INTENSIFIED CHO-PHOTOEMEROSIS FOR AGGRESSIVE NON-HODGKIN LYMPHOMAS


Introduction: the standard treatment for patients with non Hodgkin lymphoma and aggressive or adverse prognostic factors is CHOEP regimen. Nowadays, no combination chemotherapy have achieved such good results in this regimen. In our study we treated with CHOEP regimen using dose intensification (an increase of 50%), to analyze safety, feasibility, response and survival.

Methods: Between August 1997 and October 2001, 26 patients (p) with diffuse large>B-cell lymphomas and 3 T-cell lymphomas. The Ann Arbor stage bore 1 in 7, II in 3, III in 5, and IV in 12. According to the IPI, 35% p were classified as high intermediate or high risk. ECOG performance status ranged from 0 to 2. We administered ciclophosphamide mean 345 mg/m² week median 375 mg/m² week; doxorubicin mean 25mg/m² week median 50mg/m² week; vincristine mean 0.9 mg/m² week median 1 mg/m² week; prednisone mean 46.3 mg/m² week median 50 mg/m² week. In 13 p (50%) we could achieve the intensity doses p d1. Haematological toxicity was graded using common Terminology Criteria for Adverse Events (CTCAE) version 3.0. In total 60 cycles of CHOP regimen were delivered. Thirty-eight patients died during the first 3 cycles due to sepsis or massive gastrointestinal bleeding and therefore, were not evaluable for response. A favorable response was obtained in 36/34 patients (82%), including 27 patients who achieved a CR (61.4%) and 9 who achieved a PR (20.5%). The rest 8 patients exhibited refractory or progressive disease. Two of the 9 patients who exhibited PR and 1 out of the 8 patients with refractory/progressive disease achieved a prolonged CR with ASHAP-MINE (2) or ICE (1) chemotherapy regimen. Five patients (4 in CR in 1 PR) were consolidated with intensified treatment and autologous stem cell support, and 3 of them are still alive. A total of 7 patients achieved a CR (60%) in 12 months, 5 of them responding to second-line treatment. One patient developed secondary acute leukemia 7 months after the end of the treatment. In the other 4 patients secondary acute leukemia was observed 12 months after the end of the treatment. A median follow up of 30 months (range 4-115 months) 23 patients (52%) are alive and disease-free at 42-6 months (range 12-115 months) after their initial diagnosis of lymphoma.

Conclusion: In this group of patients ProMACE Cyto-BOM regimen was found effective with accepted toxicity, and deserves to be further evaluated. CHOEP-like regimens in a randomized trial, especially in patients with unfavorable features.

FIRST-LINE TREATMENT OF DIFFUSE AGGRESSIVE LYMPHOMAS WITH THE ProMACE-Cyto-BOM REGIMEN: A SINGLE CENTER EXPERIENCE


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Introduction: Non-Hodgkin's lymphomas of unfavorable prognosis do not respond well to standard first line treatment with the CHOEP-like regimens. We therefore searched for a possible improved response, by using the biologic "weak" grades IV-VII neoplasms, have been observed in 23% p and 8% presented fibrotic neoplasms, no cases of toxic death. The median follow-up time in the group of p studied was 20.7 m (range 3 - 43). A complete remission (CR) was achieved in 61% (16), partial remission (PR) in 8 p (30%); 3 patients achieved disease in 1 p (13,8 %), and one failure (3,84%). Overall response was obtained in 24 p (92%). The median event free survival (EFS) was 12,17 m. The median EFS at years 2 was 42%. The median overall survival (OS) has not been reached. After 51 months the OS was 65%.

Conclusions: This regimen of chemotherapy with intensified doses is well tolerated, and it has better results than the traditional CHO in terms of responses and OS, but only slightly better in terms of EFS. With these results we think that randomized trials are necessary, comparing standard-CHO with intensified CHOP.
A randomized CODBAM vs. CHOP front-line therapy for aggressive non-Hodgkin's lymphoma.

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Introduction: We report a randomized phase III clinical trial, the value of CODBAM continuation infusion regimen vs. the CHOP combination was studied in 85 patients with aggressive previously untreated non-Hodgkin's lymphoma. The augmented CODBAM regimen given to 44 patients consisted of daily continuous infusion of vincristine 1.0 mg/m² (maximum dose 2 mg) days 1–3, bleomycin 4 mg/m² IV push for 5 days followed by daily infusion of cyclophosphamide 100 mg/m² for 5 days followed by daily 40 mg/m² (total dose) L.V. for days 5, procarbazine 100 mg/m² on days 1–5 and cyclophosphamide 100 mg/m² on days 2, 9, 16, 23, and 30. A 3-week rest was given after every 3 cycles. Erfined doses of 10 mg/m² (total dose) and 100 mg/m² (total dose) for cyclophosphamide were given if tolerated. After these 4 cycles, patients were re-evaluated and treated with 3 more courses of CHOP regimen plus oxaliplatin given at 100 mg/m² IV. Start infusion over one hour daily for 3 days. Current regimen was repeated every 3 weeks. CODBAM was given to 41 patients as described previously.

Results: Nineteen patients were males and forty were females. Their ages ranged from 19 to 70 (median 45 years). Most of the patients had diffuse large cell lymphoma (79 cases). Four patients (4%) presented with stage I, 12 (72%) with stage II, and 18 (50%) with stage IV disease. Sixty-four (71%) were categorized as having PI of 0.4 to 26(29%) as PI score of more than 2. The different clinicopathological characteristics including PI were comparable in the two groups. Complete remission (CR) was achieved in 39 (87%) and 13 (75%) of the 45 and 44 patients for both the CHOP and CODBAM regimens respectively. The 2-year event-free and overall survival rates were 59% and 81% for the CHOP, and 55% and 63% for the CODBAM combination (P 0.65 and 0.6 for the event-free and overall survival rates respectively). Toxicities were comparable in both groups; however, non-dose-related deaths occurred more commonly in those receiving the CODBAM regimen.

Thus, a may be concluded that continuous infusion augmented CODBAM chemotherapy did not improve treatment outcome over that of the CHOP combination for aggressive non-Hodgkin's lymphoma patients.

A PILOT STUDY WITH AN ORAL CHEMOTHERAPY REGIMEN (CIEP) IN THE TREATMENT OF DIFFUSE LARGE CELL LYMPHOMA (DLCL) IN ELDERLY PATIENTS: AN INTERIM REPORT FROM ITALIAN LYMPHOMA INTERGROUP (ILI)

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Introduction: We want to evaluate the feasibility and the efficiency of an oral chemotherapy regimen in order to reduce the days of hospitalization, or even time spent as outpatients and to improve the quality of life of elderly patients.

Methods: From April 2000 to December 2001 we enrolled 52 patients who were over 65 years old and affected by DLCL. In advanced stages. They were treated with the oral regimens CIEP: Cyclophosphamide 200 mg/m² days 2-4, Idarubicin 8 mg/m² days 1–3, Prednisone 30 mg days 1-5. The number of treatment courses was 3. The frequency of treatment was every 21 days.

Radiotherapy on the residual masses was optional. The use of G-CSF was optional.

Oral Idarubicin was provided by Pharmaceuticals.

Results: Median age was 75 (65-91), 11 patients were in stage II with bulky disease, 23 patients were in stage III, 18 patients were in stage IV. 28 patients (54%) had an elevated LDH. On the 36 patients evaluated for a response: 16 (44%) obtained a CR, 8 (22%) obtained a PR and 12 (33%) had a progression. On 24 patients who had a response (CR + PR) only 5 (25%) relapsed. With a median follow-up of 8 months, 34 patients (65%) are still alive, 12 are in CCR, 13 patients presented side effects of grade 3-4 and there were two toxic deaths (ventricular fibrillation and hemorrhage).

Only 4% of patients completed their treatment within the time scheduled.

Conclusions: CIEP seems to be a good tolerated regimen. The most important issue for its feasibility is represented by the high number of tablets which the patients must take because cyclophosphamide is available only in a low dosage formulation (50 mg).

The results in terms of remission rate is not far from the golden standard, but a too high number of early relapses suggests the possibility that the oral doses of CIEP must be increased to achieve a better result.

PROTOFUSED INJECTION OF EPIRUBICIN AND VP-16 IN POOR RISK ELDERLY PATIENTS WITH AGGRESSIVE NHL AND SEVERE CARDIAC COMORBIDITY

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Introduction: Severe cardiac comorbidity prevents several elderly patients with aggressive NHL, from receiving adequate anthracycline-based best treatment, lowering their chances of a durable clinical response. The use of less cardiotoxic doxorubicin analogues coupled to alternative pharmacologic approach for drug delivering may represent a valuable strategy for this subset of patients. The present study evaluates the efficacy and tolerability of CEVOP-8 regimen incorporating continuous intravenous infusion of Epirubicin and VP-16 as front-line therapy for elderly pts with severe cardiac comorbidity and poor IPI score.

Methods: Eleven pts ineligible for standard anthracycline-based induction therapy (recent myocardial infarction, n=5; atrial fibrillation, n=4; ventricular tachycardia, n=3; complete left bundle branch block, n=2) and baseline 1.0VF > 45% were entered in the study. Treatment consisted of 4-6 subsequent courses, at a 3-week interval, of CTX (750 mg/m² d1, iv), VCR (2 mg d1, iv), Epirubicin (50 mg/m², 96 hrs c.i., d1-d4), VP16 (280 mg/m², 96 hrs c.i., d1-d4), BLM (150 mg, iv), DPHZ (40 mg/m², d1-5), oral, G-CSF (160 µg, dd 7-13). Clinical characteristics of pts were as follows: MF=65, median age 73 yrs (range 69-85), histology: DLBC, n=9; FL, GIL, n=1; ALC, n=1, Stage IV, n=9 (31%); 1LDH in all of the pts; bulky, n=4 (36%); E-stages ≥2, n=4 (30%); age adj. IPI, 2, n=3, IPI, 3, n=4 (36%).

Results: Four CR (36%) and 3 PR (27%) were obtained for an overall RR of 62%. Sudden death occurred in a single patient while receiving the 3rd CT course. All CRs are disease-free at a median follow-up of 10 mos (range 5-16). Of the 3 PRs, 1 remains in stable disease, 1 is under salvage CT and 1 died of progressive lymphoma. Toxicity consisted of CTC grade 4-5 neutropenia (7 pts), G4 thrombocytopenia (2 pts) and G4 anemia requiring pRBC transfusion (5 pts).

Conclusions: CEVOP-8 regimen with 96 hrs-protracted infusion of Epirubicin and VP-16 is an effective program for poor risk elderly pts with NHL aggressive histology and severe cardiac morbidity and may represent a reliable strategy for delivering CHOP like regimens.

Between 1972 and 1999, 101 consecutive adults over the age of 70 years were referred to the Department of Medical Oncology, for the management of ‘aggressive’ NHL. Data were available for 96 patients (56 women) with the following histological subtypes (Kiel classification): centroblastic (36), high grade unclassified (25), immunoblastic (22), ‘other’ (13). All patients underwent routine staging with clinical examination, CT scanning, bone marrow biopsy and routine haematology and biochemistry investigations, resulting in 28 patients with stage I disease, 22 stage II, 14 stage III and 31 with stage IV disease. The median age was 77 years (range 70-93). 88 patients were treated with curative intent and 8 managed supportively. 66 patients received combination chemotherapy according to protocols used at the time, and 22 were treated with radiotherapy (RT) with selection based on clinical findings. No patients received growth factor support. 7 patients have been lost to follow up. Nine patients are alive, with a median follow up of 5 years (range 0.6 to 11.4 years). The actuarial proportion predicted alive at 5 and 10 years is 31% and 16%, respectively. 79 patients have died; 41 of lymphoma, 17 of treatment-related causes, 5 of other malignancies, 7 of other known comorbidities, and 11 of unknown causes. 21 of 22 patients receiving RT completed planned therapy. In contrast, only 7 of 66 (12%) patients receiving chemotherapy completed the intended treatment at full dose; 15 did not due to treatment-related death, 11 due to progressive disease, and 3 due to debility at diagnosis or resulting from treatment. Despite this, 22 (33%) achieved a complete response (CR) with an overall response rate of 62%. Early stage disease was a strong predictor of treatment response, with an overall response rate in stage I of 78% compared to that in stage III/IV of 41% (p<0.001). Age examined as a continuous variable did not predict for response to treatment. In the group that responded to treatment (CR and partial response) 5 year progression free survival (PFS) was 33%. Recurrence continued after 5 years, and at 10 years the PFS was 6%. These long-term results emphasize the importance of careful selection of therapy for this patient population and confirm that it is possible to achieve long survival for a small proportion of elderly people with ‘aggressive’ NHL. Advances in supportive care and the availability of additional but less toxic therapy may improve outcome.

558


Background: A substantial part of elderly patients (with good performance) with intermediate or high grade non-Hodgkin's lymphoma (NHL) are not treated with standard chemotherapy (CHOP). (cyclophosphamide, doxorubicin, vincristine, prednisolone). NHL patients with CHOP indicate the outcome is inferior. By adding G-CSF to CHOP chemotherapy we were aiming for more patients to be treated with less toxicity.

Purpose and methods: A multicentre population based study in the south east of the Netherlands where 45 patients (10 patients in 2000 with intermediate grade stage I/II, 10 patients, with intermediate grade stage I/II, 10 patients, with intermediate and high grade stage I/II) were treated with CHOP chemotherapy and growth factor G-CSF to increase the number of patients treated according to standard protocol. We, also evaluated elderly NHL patients who were not treated with CHOP chemotherapy. Adequate therapy was defined as 6 cycles or a total of 3 cycles when complete remission was not achieved.

Results: 79 NHL patients fulfilled the selection criteria. Patients were treated with CHOP plus G-CSF treated with chemotherapy. The median age was 72 years (80-97). Of the 79 NHL patients 65 were treated with CHOP chemotherapy (82%). Thirty eight of 55 patients (58%) were adequately treated. Complete remission rate in the NHL group treated with CHOP was 67% for 45 patients. The overall 3 year survival was 57% of the patients (51% of the patients died for progressive NHL, 28% for relapse and 13% in the group who wasn't treated with CHOP). Treatment related mortality was 17% in the CHOP group. The most important reason for not treating patients with CHOP (with or without G-CSF) was poor performance (WHO 3).

Conclusion: A significant subset of patients can be treated with CHOP chemotherapy with acceptable toxicity. The combination of CHOP plus G-CSF increased the absolute number of treatable elderly patients, resulting in more (adequate) patients with complete remission and overall survival compared to our previous study.

557

RITUXIMAB AND GEMCITABINE FOR ELDERLY PATIENTS WITH AGGRESSIVE NON-HODGKIN’S LYMPHOMA
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Introduction: The standard treatment for patients with diffuse large-B-cell lymphoma (DLBCL) is cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP). Rituximab, a chimeric monoclonal antibody against the CD20 B-cell antigen, increases overall survival and event free survival in elderly patients in combination with CHOP, compared to CHOP alone. 1 Nevertheless, due to comorbidity some elderly patients are too ill to tolerate CHOP, and others relapse after standard therapy with CHOP. Gemcitabine is a new drug with activity in Non-Hodgkin’s lymphomas. The purpose of our study was to test the feasibility and efficacy of treatment of DLBCL with gemcitabine and rituximab in the elderly.

Methods: Elderly patients with either relapsing DLBCL after CHOP, or medically unfit to tolerate CHOP were treated with gemcitabine 1000 mg/m² d1/8/15, and rituximab 375 mg/m² d1/8/15/22 q28d. Four patients have been treated thus far, results of the first three are available:

<table>
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<th>Sex</th>
<th>Stage</th>
<th>FRT for first line therapy</th>
<th>Number of cycles</th>
<th>Best response</th>
<th>Follow up</th>
<th>Worst toxicity</th>
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<td>m</td>
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<td>35 months</td>
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<td>CR</td>
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<td>4</td>
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<td>13 months</td>
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<tr>
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<td>f</td>
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<td>10 months</td>
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559

ALTERNATING TRIPLE THERAPY (CHOP-MINE-ESHAP) IN LARGE CELL B PHENOTYPE, NON-HODGKIN’S LYMPHOMA: A CORRELATION WITH DISTINCT BIOLOGICAL ENTITIES.
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Aim: To study the role of alternating triple therapy regimen in patients with adult aggressive B-cell type lymphoma.

To subclassify large cell lymphomas into distinct clinicopathological subtypes.

Background: Over 50% of lymphomas are not cured by chemotherapy as a result of rapid development of resistance to chemotherapeutic agents. It has been postulated that drug resistant cells develop through spontaneous mutations in the tumor cell population before drug exposure and become a predominant population through selective pressures of drug treatment. Although formal clinical proof of this theory is still lacking current trends are to use many active non cross resistant agents as early and as intensively as possible.

Materials & Methods: Ninety Five patients have been treated with six to nine courses of CHOP-MINE-ESHAP between September 1997 to May 2000 and followed up May 2001. All patients treated were diagnosed as large cell. B phenotype NHL, having Stage I or II bulky disease (> 7 cm) or Stage III or IV disease. The histopathology was reviewed at our center and patients were characterised as follows: with bol-1 and without bol-1 (bol-2). The bol-2 blast cells and without bol-2 (bol-1).

Results: Overall response was 84.5% in evaluable patients. Eleven patients were non evaluable for response (treatment changed in 3, lost to follow up on treatment 5, mortality in 1, mortality in 2). The present status of 71 patients who achieved a response is as follows: of 40 CR patients, 33 are in CR and 7 have relapsed and of 31 PR patients, 24 are in PR and 7 have progressed. The median disease free survival is not reached for patients who responded to treatment. The Relapse free survival is 70% at 3 years for ALL patients. 70% of patients treated failed to show any significant correlation with bol-1, or bol-2. In the group of patients with blast cells and without bol-2 and c) others.

Conclusion: The overall response was 84.5% in evaluable patients. Eleven patients were non evaluable for response (treatment changed in 3, lost to follow up on treatment 5, mortality in 1, mortality in 2). The present status of 71 patients who achieved a response is as follows: of 40 CR patients, 33 are in CR and 7 have relapsed and of 31 PR patients, 24 are in PR and 7 have progressed. The median disease free survival is not reached for patients who responded to treatment. The Relapse free survival is 70% at 3 years for ALL patients. 70% of patients treated failed to show any significant correlation with bol-1, or bol-2. The bol-2 blast cells and without bol-2 and c) others. The relapse rate for each of the three cycles of CHOP-MINE-ESHAP was 7% 10% 5% after MINE, 2% after ESHAP. Six patients developed febrile neutropenia after receiving ESHAP.

Significance: In an uncontrolled setting the Relapse free survival of 70% at 3 years is encouraging, however a longer follow up and a randomized trial will be required to prove the efficacy of ATT.
560
HIGH-DOSE IFOSFAMIDE PLUS ETOPOSIDE FOR REFRACTORY OR RELAPSED AGGRESSIVE NON-HODGKIN’S LYMPHOMA.

Introduction: We designed a salvage program including infusional high-dose ifosfamide plus high-dose etoposide (IFOVEM) followed by DHAP to evaluate tolerance and efficacy in patients with refractory or relapsed aggressive non-Hodgkin’s lymphoma (NHL).

Patients and methods: From January 1996 to August 2001, 46 patients with refractory (acquired 17% or primary 39%) or relapsed (44%) NHL were included in the study. Mean time of last treatment was 9 months (range, 1-66). IFOVEM consisted of ifosfamide (10 g/m² in a 72-hour infusion on days 1-3), etoposide (150 mg/m² every 12 hours on days 1-3), and melphalan/prednisone with G-CSF. Responding patients underwent two cycles of the DHAP chemotherapy and subsequent autologous peripheral blood stem cell transplantation (APBSCT) with BEAM/BEAC conditioning.

Results: All patients showed tumour regression. Following IFOVEM, Myelosuppression was short: neutropenia (<0.5 × 10⁹/l) of 5 days (range, 2-10) and thrombocytopenia (<20 × 10⁹/l) of 0-3 days (0-35). Seventy-two patients developed neutropenic fever and 6 uncomplicated bacteremias. Four had grade 3-4 non-hematological toxicity. All but two patients proceeded to DHAP (1 received a 2nd cycle of IFOVEM and 1 had rapid progression). Overall response rate to IFOVEM/DHAP was 39% (CR 26% and PR 33%). Refractory patients had a relative risk of progression of 9.06 (95% CI 5.5-12.39) compared to relapsed patients. All refractory patients with intermediate-high or high IPI progressed. PBSC were collected after IFOVEM or DHAP in 16 and 22 patients, respectively. Twenty-seven proceeded to APBSCT (13 in CR, 14 in PR and 2 with progressive disease). Six (46%) patients autografted in PR achieved CR. With a median follow-up after transplant of 11 months (1-56), 8 patients progressed (1 alive after allogeneic transplant with reduced intensity conditioning, 2 died in apparent CR and 17 are still in CR. The overall (OS) and event-free (EFS) two-year survivals were 36% and 34%, respectively. OS and EFS at two years in patients with relapsed disease (44% and 39%, respectively) were significantly better than in those with refractory disease (29% both; P=0.05).

Conclusions: High-dose infusional ifosfamide and etoposide appears safe and effective in patients with relapsed NHL. The activity of this regimen is lower in refractory disease, especially in those with intermediate-high or high IPI. Such patients should receive alternative investigational therapies.

561
Dexasone in the treatment of CHOP-resistant NHL.
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It was shown that dexasone has higher antileukemic effect than prednisolone. So, the aim of this study was the evaluation of efficacy of Dexasone in CHOP-resistant NHL patients.

Patients and Methods: 66 -CHOP-resistant patients were included. According to the Kiel classification 48 cases had low, 18 cases had high grade malignancy. Bone marrow was involved in all patients. One group of patients were further treated with COPBLAM and ASHAP, MAD, Dexa-BEAM, the other (45) by pulse therapy of Dexasone 40 mg/dl p.o., nor less 3 cycles.

Results: By NHL CHOP-resistant patients were sensitive to Dexasone, the results were comparable to intensive regimen, p>0.05. We have CR+PR by low grade NHL -36.4%, by high grade NHL -50%. The median duration of the effect of Dexasone therapy was about 12 months by low NHL, 2 months by high grade NHL. They had not major complications on Dexasone therapy.

Conclusion: Pulse therapy of Dexasone is the variant of effective palliative therapy for CHOP-resistant low grade NHL. They had short efficacy for CHOP-resistant high grade NHL patients.

Key words: NHL, dexasone.

562
A COMBINATION OF GEMCITABINE, IFOSPHAMIDE, AND VINORELBINE IS ACTIVE IN RELAPSING AND REFRACTORY LYMPHOMA, BOTH AS ANTITUMOR AND MOBILIZING REGIMEN.
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Background and Purpose: To evaluate the activity of a gemcitabine-containing regimen in relapsing or resistant malignant lymphoma and its capacity to mobilize myeloid and/or dendritic cell progenitor cells (PBPC).

Patients and Methods: This study was conducted on 21 patients (median age: 50 years), affected with Hodgkin’s disease (17) or non-Hodgkin’s lymphoma (4). Six patients had a resistant disease and 13 had relapsed after doxorubicin-containing regimens (8 were in their first relapse); 57% of patients had received more than 2 prior CT regimens. The CT regimen (GEMOX) consisted of gemcitabine 800 mg/m² i.v. over 30 days 1 and 4, ifosfamide 2000 mg/m²/day i.v. over days 1-4 and vinorelbine 20 mg/m²/day i.v. on day 1 and prednisone 100 mg/day for 4 days.

To mobilize PBPC, IGE was followed by G-CSF (5 ug/kg).

Results: The overall response rate to IGE was 72% and CR rate 29%. All remitters were in first relapse; seven of 13 patients achieving partial or complete response, have progressed, so far (34%), with a median progression-free interval of 11 months (range: 1-18). After a median follow-up of 18 months, 13 patients are alive (5 with no evidence of disease) and 8 died of disease progression. WHO grade III-IV hematological toxicity was documented in 52% of cases, with no life-threatening episodes; fever occurred in 52%, cutaneous rash in 24% and lung toxicity (alveolitis) in a single patient. PBPC mobilization was successful in 14 of 20 patients (90%), with leukopheretic collection of median 8.9 x 10⁹/kg CD34+ cells and 83 x 10⁹/kg CFU-GM cells; 50% of patients achieved the threshold yield of 4 x 10⁹/kg CD34+cells with a single leukopheresis and a significant difference was found according to the number of CT regimens received before IGEV therapy.

Conclusions: The IGEV regimen is active as salvage therapy in Hodgkin’s disease and has a good PBPC mobilizing capacity, even in heavily pretreated patients.

563
GEMCITABINE, DEXAMETHASONE, CISPLATIN, GYP (GDP) CHEMOTHERAPY FOR RELAPSING OR REFRACTORY NON-HODGKIN’S LYMPHOMA (NHL) AND HODGKIN’S DISEASE (HD).
National Cancer Institute of Canada Clinical Trials Group, Kingston, Ontario, and Eli Lilly Canada, Toronto, Ontario, Canada.

Introduction: Gemcitabine (G) is active as a single agent in NHL and HD and demonstrates synergy with cisplatin (P) in vitro. The optimum salvage therapy for NHL and HD prior to stem cell transplantation (ASCT) or for those who are not transplant candidates remains to be defined.

Patients and Methods: From Feb to Dec 2001, 38 patients (pts) were enrolled on this phase II study (NHL 28: 25 large B cell, 2 CD20+; 1 T cell rich B cell; HD 10). All pts had relapsed after or failed to respond to anthracycline-based chemotherapy (CHOP for NHL, ABVD for HD). Protocol treatment was given on an outpatient basis: G 1000 mg/m² IV d1 & 8, dexamethasone 40 mg po d1-4, P 75 mg/m² day 1 every 3 weeks. Response was assessed after 2 cycles; eligible pts proceeded to stem cell collection and ASCT; respondents otherwise continued for up to 6 cycles. Median age: NHL: 58 (range 18-76); HD: 34 (range 19-57). IPI risk factors at relapse (NHL pts): 0/4, 1/5, 2/6, 3/7, 4/2, 5/9; stable disease or progression on primary therapy: NHL: 4, HD: 0.

Results: Data on response after 2 cycles are available for 29 pts: 21 NHL: 3 CR, 9 PR (response rate (RR) 57%); 8 HD: 7 PR (RR 87%). Nine NHL and all 8 HD pts proceeded to ASCT. Hematologic toxicities observed (33 pts: 72 cycles) were: neutropenia grade 3: 10 pts, grade 4: 6 pts; thrombocytopenia grade 3: 5 pts, grade 4: 2 pts. Five pts experienced febrile neutropenia. One pt died of complications of tumor lysis syndrome after cycle 1. Accrual to both cohorts continues; updated response and toxicity data will be presented.

Conclusions: This preliminary analysis suggests that GDP is an active regimen in relapsing and refractory NHL and HD, and can be given in the outpatient setting with acceptable toxicity. These early results compare favourably with inpatient cisplatin-based regimens and a randomized phase III trial is planned.
A GEMCITABINE, CISPLATIN, AND DEXAMETHASONE COMBINATION IN PATIENTS WITH MULTIPLE RELAPSED HODGKIN’S AND NON-HODGKIN’S LYMPHOMA

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Introduction: Patients with Hodgkin’s (HL) or Non-Hodgkin’s Lymphoma (NHL) often undergo multiple treatments with progressive development of chemoresistance. This study examines the activity of Gemcitabine in combination with moderate doses of Cisplatin and Dexamethasone for the treatment of relapsed HL and NHL patients.

Methods: Patients enrolled in this phase II single study received Cisplatin 35 mg/m² on day 1, Dexamethasone 20 mg on days 1-4, and Gemcitabine 800 mg/m² at a constant infusion rate of 10 mg/m²/min on day 1. The cycle was repeated every two weeks. Cisplatin dose escalation by 100 mg/m² was allowed.

Goals: The goals of this study include: (1) to ascertain the maximum tolerated doses of Gemcitabine in combination with fixed doses of Cisplatin and Dexamethasone in the treatment of relapsed NHL and HL; and (2) to assess the response rate, duration of response, and progression-free survival.

Results: Twenty-two patients enrolled; ages 25-77 (median 52.5), presenting with HL: 7, T-cell NHL: 6, B-cell NHL: 9 (Diffuse large B-cell NHL: 2, Follicular lymphoma: 2, Small lymphocytic lymphoma: Chronic lymphocytic leukaemia: 2, Mantle cell lymphoma: 1). Patients had a median of 4-10 prior treatments in 27 months (10-105) since initial diagnosis. 10 had relapsed following high dose chemotherapy and auto (9) or allo (1) SCT. Sixteen patients had completed chemoradiotherapy as a prior treatment. Patients received a median of 2.5 (1-17) cycles. Of the 20 evaluable patients, two achieved a complete response, eight a partial response, and two had stable disease, for an overall response rate of 50.0%; responses favored NHL (4/6 pts responded). Median time to progression for responders was 6.5 months (2-66) and 3 months (1-26) for all. Dose escalation was possible in three patients whereas dose reductions were required in three others. Grade IV thrombocytopenia or neutropenia was noted in 47% and 21%, respectively. Grade 1-2 toxicity in 3 patients. These results suggest that Gemcitabine-based combination therapy is useful in heavily pretreated lymphoma patients.

COMBINATION OF GEMCITABINE AND OXALPLATIN (GEMOX) IN REFRACTORY AND RELAPSED NHL

G. Corazza, G. Capobianco, P. Frigeri, F. Russo, G. Marrazzo, A. Pinto

Introduction: Preliminary and clinical studies have indicated a synergistic effect for the combination of Gemcitabine and Oxaliplatin in solid tumors. This has been attributed to different mechanisms of action and absence of overlapping toxicities.

Methods: Phase two study was designed to assess the efficacy and toxicity of Gemcitabine/Oxaliplatin in relapsed refractory NHL. Gemcitabine regimen consisted of 125 mg/m² iv (d 1, 8) and Oxaliplatin 120 mg/m² iv d 2. Twenty patients have been so far enrolled and are evaluable for response. Median age = 68 yrs (range, 46-81) aggressivity histology = 16 (DLBCL, 10, PTCL-2, MCL-2, Indolent = 4 (SLL-2). MZL=1, LPL=1). Two pts were primary refractory, 5 progressed from a previous PR, 3 were in 1 relapse, 8 were in 2 relapses and 1 was in relapse post-ASCT. ECOG PS=1 (3), PS=0 (6) and PS=2 (4) (n=3).

Results: A total of 80 courses were delivered (median 4, range 2-8). Four pts achieved a CR (20%, 95% CI: 6-64) and 8 pts a PR (40%, 95% CI: 19-64) for an overall RR of 60% (95% CI: 36-81). All CRs had a DLBCL histology. Median CR and PR durations were 4+ and 3+ mos, respectively. Among the 8 pts older than 70 yrs, 1 CR and 4 PRs were achieved upon a total of 32 delivered courses. Interestingly, 2 (good) PRs were obtained in MCL pts. Two CR pts relapsed at 3 and 4 mos. CTC G3-4 neutropenia and G3 thrombocytopenia were recorded in 21% and 9% of the administered courses, respectively. RBC transfusions were required in 4 patients. Extrahematologic toxicity was negligible.

Conclusions: GEMOX regimen displays a promising activity and acceptable toxicity, in the salvage and palliative setting of heavily pretreated pts with relapsed/refractory NHL. It can be safely employed in elderly patients, whose treatment of recurrent NHL may reveal challenging due to comorbidity, functional status and toxicity from previous chemotherapy. A more prolonged treatment may be needed to further improve the disease free survival.

IFOSFAMIDE, EPIRUBICIN AND ETOPOSIDE (IEV) REGIMEN AS SALVAGE AND MOBILIZING THERAPY FOR RELAPSED/REFRACTORY LYMPHOMA PATIENTS


Introduction: Therapy for relapsed/refractory lymphomas should be based only on drugs not included in the front-line chemotherapy regimens. We adopted the strategy of using salvage chemotherapy to debulk disease and simultaneously mobilize stem cells, using a regimen based on ifosfamide and etoposide (drugs not usually used for front-line treatment).

Methods: A three-drug combination of ifosfamide, epirubicin and etoposide (IEV) was used to treat 62 patients with relapsing or refractory aggressive non-Hodgkin’s lymphoma (NHL; n=51) or Hodgkin’s disease (HD; n=11). Forty-five patients were studied for the feasibility of peripheral blood stem cells (PBSC) harvesting. The median duration of the response was 9 months (range, 2 to 14 months). Mobilization was successful in 33 of 45 (73%) patients. Among the 45 patients who proceeded to autotransplant (27 (60%) were in CR status after the autograft; 23 of 45 (51%) patients are currently in continuous CR with a median follow-up of 25 months (range, 10-58 months); the relapse free survival curve is 83% at 60 months. Clinical and hematologic toxic effects were mild.

Conclusions: Our results indicate the efficacy of the IEV regimen in inducing a good remission rate. IEV is a predictable and highly effective mobilization regimen in relapsed/refractory patients with aggressive NHL or HD.
A COMBINATION OF IDARUBICIN, CIS-PLATIN, HIGH-DOSE CYTARABINE AND HIGH-DOSE IP+AD (IPAD) IS ACTIVE IN LYMPHOMA, WITH GOOD MOBILIZING CAPACITY. E. Brusamolino, M. Bonfichi, L. Gargantini, C. Castagnola, S. Caberlon, C. Baraté, L. Vanelli, P. Zappasodi, E. Morra, M. Laezzurri. Division of Hematology, IRCCS Policlinico San Matteo, University of Pavia, and Niguarda Hospital, Milan, Italy

Purpose: To report on IPAD activity as salvage chemotherapy in non-Hodgkin’s lymphoma and as consolidation and mobilizing regimen in front-line therapy of poor-risk aggressive lymphomas.

Patients and Methods: IPAD regimen consists of idarubicin 12mg/m2 on day 1, cis-platin 50mg/m2/day, continuous infusion on days 1 and 2, cytarabine 2g/m2/12hrs, on day 3 and dexamethasone 20 mg/day for 3 days. IPAD regimen was part of a salvage approach in 26 pts with relapsing (12) or resistant (14) lymphoma. Besides, two cycles of IPAD were used after VACOP-B in 14 poor-risk lymphoma in a front-line program. In 19 pts, IPAD was followed by G-CSF to mobilize peripheral blood progenitor cells (PBPC). Median age at IPAD was 48 yrs; histology included diffuse large B-cell (31), follicular (6) and peripheral T-cell (3) lymphoma. All pts given salvage IPAD had prior doxorubicin-containing regimens and 50% had two or more prior CT regimens.

Results: Overall response rate to salvage IPAD was 58% and CR rate 23%; 80% of pts achieving disease control have progressed, with a median 5-mos progression-free time (range: 2-16+). On the other hand, two courses of IPAD, given in front-line program, induced CR in 3 of 9 pts resistant to prior VACOP-B. WHO grade III-IV hematologic toxicity occurred in 80% of cases, with a single fatal infectious complication in the salvage group. Non-hematologic toxicity included nausea and vomiting (33%), fever (28%), diarrhea (8%) and reversible renal toxicity in a single patient. PBPC mobilization was successful in 17 of 19 pts (89%), yielding a median 7.1 x 10^9/Kg CD34+ cells with a mean 1.7 leukapheresis per patient.

Conclusions: The IPAD regimen is active in lymphoma and can be integrated in front-line or salvage programs; toxicity is manageable and its mobilizing capacity may be instrumental for myeloablative approaches.

Induction of durable second remission in aggressive non-Hodgkin’s lymphoma with Rituximab (anti-CD20) monotherapy, continuously maintained with monthly Rituximab combined with chlorambucil.

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Department of Hematology and *Blood Bank Unit, Wolfson Medical Center (affiliated with the Medical School of Tel-Aviv University), Holon, Israel.

Age over 65 and advance stage are poor prognostic factors in aggressive non-Hodgkin’s lymphoma (NHL). Salvage treatment with conventional chemotherapy in relapsing disease is associated with considerable toxicity and is only occasionally curative. High-grade non-Hodgkin lymphoma is a highly aggressive disease, which is particularly sensitive to anti-CD20 antibody as monotherapy is capable of inducing a second remission in relapsing low-grade B-cell NHL. A significant survival advantage has been demonstrated adding Rituximab to a standard chemotherapy in elderly patients with aggressive NHL.

We recently treated a 75 year-old female patient with stage III-B diffuse large non-Hodgkin’s lymphoma with immunoblastic features and last progression of D12 resulting from a paravertebral mass, who relapsed with bulky lymphadenopathy after a short-lasting remission induced by local irradiation to the area of D12 followed by 6 courses of CHOP chemotherapy. A second remission has been achieved with Rituximab monotherapy and maintained for 12 months with Rituximab at a dose of 375 mg/m2, combined with oral chlorambucil 15 mg/day over 4 days once a month. There were no toxic effects to this treatment and no hospitalizations were required. Rituximab given in a maintenance set-up may provide an effective and non-toxic therapeutic approach for patients with relapsing high grade NHL, especially when aggressive chemotherapy with or without stem cell transplantation is not a feasible option. This treatment has to be verified in extended clinical studies.

HIGH DOSE SEQUENTIAL CHEMOTHERAPY (HDSC) AS SALVAGE THERAPY OF PATIENTS WITH MALIGNANT LYMPHOMAS: PROGNOSTIC FACTORS AND CLINICAL OUTCOMES.


Hematology Department, BMT Unit – University of Verona, Italy

We revised 100 patients with resistant or relapsed malignant lymphoma after Doxorubicin-containing regimens. All underwent high dose chemotherapy including CTX 7 g/m2, MTX 8 g/m2, VP-16 2 g/m2 and Mitoxantrone 60 mg/m2+L-PAM 140 mg/m2 followed by PBSC rescue. A debulking second-line chemotherapy was given when necessary before high dose HDSC. Median age was 42 (range 20-65), and 53 were males. Therapy patients were affected by Hodgkin Lymphoma (HL), 16 by advanced follicular lymphoma (FL), and 54 by high-grade non-Hodgkin lymphoma (HG-NHL). Among these, 41 had B-cell, and 13 T-cell lymphomas. Overall, at the time of HDSC, 58% had an asymptomatic IV, 41% had bone marrow involvement, 51% had B-symptoms, 32% had ECOG ≥2, 56% had high serum LDH, 34% had extranodal localizations. Before transplant 67 patients still had evidence of disease (54% R, 23% CR).

Results: With a median follow-up of 49 months (range 12-103), 57 patients are alive, of whom 50 are in complete remission (CR). After HDSC 93 patients achieved CR. Survival (OS) and Disease-Free Survival (DFS) at 5 years for all patients was 50% and 46%, respectively. When divided according to histologies, 5-years OS was 56%, 73% and 41% (p<0.03), and DFS was 56%, 49%, and 42% (p<0.02) for HD, FL and HG-NHL, respectively. Treatment related mortality was 1%. Overall, at the time of HDSC, <1% patients had an asymptomatic IV, 41% had bone marrow involvement, 51% had B-symptoms, 32% had ECOG ≥2, 56% had high serum LDH, 34% had extranodal localizations. Before transplant 67 patients still had evidence of disease (54% R, 23% CR).
AN "AGE-ADJUSTED" HIGH DOSE CHEMOTHERAPY (HDC) WITH ASCT ALLOWS ADEQUATE BPCF YIELD WITH LOW TOXICITY AND PROMISING RESULTS IN ELDERLY PATIENTS WITH AGGRESSIVE NON-HODGKIN’S LYMPHOMA (NHL).

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1Istituto di Ematologia, Torino, Italy; 2Istituto di Anatomia, Università Cattolica, Rome, Italy

Introduction: elderly patients (> 60 yrs) are usually considered not eligible for HDC. However, most of them could tolerate ASCT with an "age-adjusted" HDC regimen. Patients and Methods: 56 aged between 61-70 yrs with aggressive NHL in relapse/progression or at diagnosis were treated with A: 6 x weeks of F-VEBEC chemotherapy (prophylaxis). A blast 2: 6 x weeks of Autologous hematopoietic progenitor cell transplantation (ASCT) conditioned by BEAC regimen B (carmustine 240 mg/m2 x 2 + vincristine 2 mg/m2 + cyclophosphamide 600 mg/m2 x 2 + adriamycin 60 mg/m2 x 2 + cyclophosphamide 1000 mg/m2 x 2 + methotrexate 1500 mg/m2 x 3) alternating with MHD-MACHOP (carmustine 240 mg/m2 x 2 + vincristine 2 mg/m2 + cyclophosphamide 800 mg/m2 x 1 + doxorubicin 60 mg/m2 x 2 + cyclophosphamide 2000 mg/m2 x 2 + methotrexate 500 mg/m2 x 3) to be repeated every 21 days for a maximum of 6 courses. Patients in complete (CR) or partial remission (PR) underwent ASCT collection with G-CSF and for patients who failed PBSC collection an attempt from bone marrow was allowed. ASCT was performed using BAVC as conditioning regimen (BCNU, cyclophosphamide, etoposide, carboplatin). Eligibility criteria included: IPI I and H age less than 60 years old, absence of previous treatment, HIV negativity, absence of important comorbidities.

Results: Twenty-three consecutive untreated patients (14 III, 9 II risk), median age 37 years (range 20-59) have been registered into the study so far. Histological subtypes were B-DLCL (42/2), B mediastinal (5/23), ALC (4/23), peripheral unspecified (2/23). At present, 14 patients completed the induction therapy (3 received involved field RT). Eight patients did not perform SC harvesting because of failure (1), refusal (1), no response to induction therapy (6). Eleven patients did not complete the therapeutic protocol with ASCI pre-treated and 4 completed the treatment while on chemotheraphy (1/2). After HDC-MACHOP + RT we registered 21 CRs (43%), 7 TPRs (33%) and 3 non responders (6%). During HDC-MACHOP therapy grade III-IV anemia, thrombocytopenia and neutropenia were observed in 8/21, 12/21 and 20/21, respectively. Major infectious complications developed in 3 patients. Two patients had grade III and IV mucositis each. After a median follow-up from diagnosis of 24 months (range 1-37) 13 out of 20 evaluable patients (30%) had completed the lymphoma progression.

Conclusions: These results support the hypothesis that an intensive therapeutic program could be more effective for III and II IPI NHL than standard treatment.

FEASIBILITY OF A SEQUENTIAL TREATMENT BY CHOP AND DHAPE PLUS MITOXANTRONE FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN MANTLE CELL LYMPHOMA (MCL).

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1Hôpital Saint-Jean, Strasbourg, France; 2Hôpital Saint-Louis, Paris, France; 3Hôpital Européen, Garches, France

We have shown that a sequential chemotherapy by CHOP and DHAPE followed by ASCT is feasible. Two hundred and thirty patients with MCL have been enrolled in this study. Inclusion criteria were age ≤ 70 years, a good general status and an expected survival of > 1 year. The treatment was given as follows: CHOP regimen (doxorubicin 50 mg/m2, cyclophosphamide 750 mg/m2, vincristine 2 mg/m2 and prednisone 1000 mg/m2) given on days 1, 8, 15 and 22 of a 28-day cycle for 6 cycles. Mitoxantrone 7.5 mg/m2 was given on days 1 and 15 of cycles 1, 3 and 5. Patients were randomized in 2 groups: patients in group A received 3 cycles of DHAPE regimen comprised of vincristine 1.4 mg/m2, dexamethasone 40 mg/m2, Adriamycin 25 mg/m2 and etoposide 100 mg/m2 on day 1 and 15 and 29 days of a 28-day cycle. Patients in group B were randomized in two groups: TBI or Gamma knife + ASCT. All patients were assessed for response to CHOP and DHAPE regimen. We have shown that a sequential chemotherapy regimen followed by ASCT could be feasible. It is necessary to determine the optimal number of cycles of DHAPE regimen. Further studies are needed to determine the optimal schedule of ASCT.
DOUBLE INDUCTION FOLLOWED BY SEQUENTIAL HIGH DOSE THERAPY INCLUDING TREOSULAN, MELPHALAN AND THIOTEPA WITH AUTOLOGOUS STEM CELL TRANSPLANTATION FOR RELAPSED OR REFRACTORY HIGH-GRADE LYMPHOMA

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Introduction: To improve the prognosis of relapsed and refractory high-grade lymphoma patients (pts) the East German Study Group Hematology and Oncology (OSHO) started a phase II trial choosing a new sequential high-dose approach.

Treatment plan: For remission induction and stem cell mobilisation, 1 cycle of DecaBEAM and 1 cycle of etoposide at 60 mg/m² are given. The first high dose therapy (HDT) combines treosulam with melphalan at 140 mg/m² total dose, the second high dose regimen combines treosulam with thiopeta at 250 mg/m², both followed by autologous peripheral stem cell transplantation. Treosulam dosage is studied at 30, 39, and 48 g/m² total dose per high dose cycle, corresponding to dose levels I to III.

Results: So far, 12 pts (25-59 yrs, stages II: 3, III:6, IV: 3 pts) have been enrolled, 7 of these with relapsed and 5 with primary refractory disease. Histology included diffuse large cell and anaplastic large cell lymphomas, follicular lymphomas grade III (1 pt), Hodgkin and plasmocytoid T-cell lymphomas. Five pts completed the protocol with two HDT cycles, 1 pt declined the 2nd HDT due to previous stomatitis grade IV. 3 pts are still under therapy, and four pts never received the therapy.

Table: No. of pts with *III and IV non-hematological toxicities besides sepsis

<table>
<thead>
<tr>
<th>CTC</th>
<th>DecaBEAM</th>
<th>Etoposide</th>
<th>HD Treo + Mel</th>
<th>HD Treo + Thio</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>12</td>
<td>9</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>+ III</td>
<td>3</td>
<td>1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>+ IV</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Stomatous</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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</table>

* III toxicities during 1st and 2nd HDT included stomatitis, infections and elevated liver TA (1 pt). Mean hematologic recovery to >10000 and >20 g/dl was (8-9) and (11-12) days after 1st HDT, (9-11) and (12-14) days after 2nd HDT. Five pts died due to disease progression. Of these, 3 died after induction therapy, 2 pts and 4 pts after DecaBEAM and 6 pts after 2nd HDT. No toxic death occurred. Five of 6 pts with progressive disease were primary refractory. 7/12 pts died of CR, of which relapsed, each 4 months after therapy (1 primary refractory disease and 1 follicular lymphoma grade II-D). Three of the CRs were attained only after HDT. Conclusions: Sequential HDT at dose level I was feasible and effective. Since the maximum tolerable toxicity of treosulam within this protocol has not yet been reached the dose escalation study will continue.

HIGH-DOSE-CHOP/ESHAP FOLLOWED BY AUTOLOGOUS STEM-CELL TRANSPLANTATION (ASCT) VS. CHOP FOR HIGH-RISE AGGRESSIVE LYMPHOMAS: A CASE-CONTROL STUDY


Objective: To compare the results in terms of response, toxicity and survival of the intensive regimen high-dose-CHOP/ESHAH + ASCT with case-matched historic controls from the same institution treated with CHPOP.

Patients and Methods: 33 pts <65 yrs in stages II-IV diagnosed between 1997 and 2001 in a single institution with either 1) diffuse large B-cell lymphoma (N=23) with high-risk (N=15) or intermediate-risk (N=8) plus high serum β2-microglobulin (N=9, N=8, or 2) peripheral T-cell lymphomas (N=10) who were included in a phase II trial (3 courses of high-dose CHOP/ESHAP) followed by ASCT) were matched with historic case-control patients diagnosed and treated with CHOP in the same institution between 1991 and 1997. The matching criteria included the same age, gender, histologic subtype, and risk according to IPFI.

Results: No differences were found between the two groups regarding the main initial features, including B-symptoms, PS, stage, extranodal involvement, and serum LDH and β2-microglobulin. Early response, death, failure-free (FFS) and overall survival (OS) are detailed in the table:

<table>
<thead>
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<th>CR rate</th>
<th>Early death</th>
<th>Year 2 FFS</th>
<th>Year 2 OS</th>
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<tbody>
<tr>
<td>High-CHOP/ESHAP</td>
<td>+ ASCT</td>
<td>54%</td>
<td>6%</td>
</tr>
<tr>
<td>Control (CHOP)</td>
<td>+ ASCT</td>
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<td>9%</td>
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Median follow-up of active patients was 1.9 and 4.4 years for intensive regimen and CHOP, respectively. Patients treated with high-dose CHOP/ESHAP showed more often grade 2/3 neutropenia and thrombocytopenia than controls. Finally, severe infection was observed in 20% and 4% of courses of high-dose CHOP/ESHAP and CHOP, respectively.

Conclusions: Although no significant differences were found in terms of response, patients treated with the intensive regimen showed a trend for better FFS and OS than those receiving standard CHOP.

FURTHER EVALUATION OF A SEQUENTIAL CHEMOTHERAPY BY CHOP AND DEXAMETHASONE FOLLOWED BY HIGH-DOSE THERAPY WITH STEM CELL TRANSPLANTATION IN MANTLE CELL LYMPHOMA


Introduction: Mantle-cell lymphoma (MCL) is a distinct clinicopathological entity with a poor prognosis. Methods: We have conducted a prospective study in patients with MCL less than 65 years old to evaluate a therapeutic strategy in which CHOP polychemotherapy was followed by DHAP if CHOP failed to induce complete remission. Responding patients then proceeded to an intensification therapy with autologous peripheral blood stem cell transplantation (APBSCT). Twenty-eight children with newly diagnosed poor-risk MCL were included.

Results: After 4 cycles of CHOP regimen, 2 complete response (CR) were obtained (7%) and 14 (50%), 5 (18%) and 7 (25%) patients achieved partial (PR), minor (MR) and no response, respectively. One patient died from septic complications during CHOP induction. The two patients in CR after CHOP underwent intensification with TBI, high dose cyclophosphamide-etoposide and APBSCT. The twenty-five other patients received DHAP after which a response rate of 92% (21 CR), 8 PR (3%) was observed. Two patients had progressive disease. The twenty-three responding patients received high dose therapy (TAM Roberts: TBI-Cytarabine-Melphalan) followed by APBSCT. One of the two partial responding patients entered in CR after TAME. After a median follow-up of 15 months (range, 30-81), ten patients have relapsed and 24 patients are still alive. Conclusion: Our data confirm with longer follow-up that 1) CHOP followed by DHAP allows a large proportion of patients to proceed to high dose therapy in complete remission. 2) Consolidation therapy including total body irradiation and high dose Ara-C followed by APBSCT probably improves event free survival. A multicentric study testing the anti-CD20 therapy continue to such strategy is on going.

HIGH-DOSE-CHOP PLUS ESHAP FOLLOWED BY AUTOLOGOUS STEM-CELL TRANSPLANTATION (ASCT) FOR HIGH-RISK AGGRESSIVE LYMPHOMAS

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Objective: To analyze response, toxicity and survival in high-risk aggressive lymphomas receiving the intensive regimen high-dose-CHOP+EHHAP followed by ASCT.

Patients and methods: In an ongoing phase II study, pts <65 yrs in stages IV with either 1) diffuse large B-cell lymphoma (DLBCL) or high-grade non-Hodgkin lymphomas or 2) peripheral T-cell lymphomas (PTCL). Followed by ASCT) were matched with historic case-control patients diagnosed and treated with CHOP in the same institution between 1991 and 1997. The matching criteria included the same age, gender, histologic subtype, and risk according to IPFI.

Results: No differences were found between the two groups regarding the main initial features, including B-symptoms, PS, stage, extranodal involvement, and serum LDH and β2-microglobulin. Early response, death, failure-free (FFS) and overall survival (OS) are detailed in the table:

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Median follow-up of active patients was 1.9 and 4.4 years for intensive regimen and CHOP, respectively. Patients treated with high-dose CHOP/ESHAP showed more often grade 2/3 neutropenia and thrombocytopenia than controls. Finally, severe infection was observed in 20% and 4% of courses of high-dose CHOP/ESHAP and CHOP, respectively.

Conclusions: Although no significant differences were found in terms of response, patients treated with the intensive regimen showed a trend for better FFS and OS than those receiving standard CHOP.
RITUXIMAB, CD34+ CELL SELECTION AND HIGH-DOSE CHEMOTHERAPY IN ADVANCED STAGE MANTLE-CELL LYMPHOMA. A PILOT STUDY.

G. Martini,

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G. Cittadini,

A. Vanazzi,

C. Rambasco,

C. Corsini,

F. Bertoni,

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Introduction: Mantle-cell lymphoma (MCL) is a CD20+ malignancy currently incurable with standard therapy. As a single-agent, rituximab has moderate activity in MCL with 30% RR and a median duration of response of 1.4 y (Foran et al. 2007). When CHOP and rituximab were used as initial MCL treatment, Howard et al. (1999) reported a 46% CR rate, but patients (pts) subsequently relapsed. Here we report about the feasibility of a program involving rituximab, CD34+ cell selection and intensive chemotherapy in patients with advanced and refractory MCL.

Methods: We treated so far 8 pts, (5 newly-diagnosed, 3 previously-treated), median age 55 y (45-62), 7/8 in stage IV. All pts had bic-1-positive mantle, 2 had bulky disease, 2 had leukemia disease. Median 21% in 5.8. Pts received rituximab (375 mg/m²) at the first day of each treatment consisting of 2 CHOP-like, CTX 4 g/m² and G-CSF to collect >2x10^6 CD34+ cells/Kg (apheresis were processed by Clinimacs for CD34+ cell purification), 2 intensified ESHAP and CD34+ cell reinfusion after IDA 15 mg/m² and L-PAM 180 mg/m². Results: Before transplant, 4 pts achieved a CR, and 4 were in PR. After the combined in vivo and in vitro purging, 7/8 pts had bic-1-negative CD34+ cell collections. In one pt the CD34+ cell collection failed. After a median follow-up of 18 months (9-32), 7/8 pts were in CR (confirmed by bic-1 PCR), the pt who failed to collect bic-1-negative CD34+ cells relapsed 6 months after achieving a CR. Infective complications: 3 pneumonia, 2 CVC thrombosis. Remissions in advanced or refractory MCL patients. A longer follow up is needed to confirm the clinical relevance of this regimen.

FEASIBILITY OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION (allog-HSCT) WITH A REDUCED-INTENSITY (RI) CONDITIONING REGIMEN FOR NON-HODGKIN Lymphoma (NHL)

T. E. Tanizomei,

E. Kusumi,

T. Hamaki,

K. Yoji,

Y. Ueyama,

S. Miyakoshi,

S. Morinaga,

M. Kamii,

K. Kojima,

A. Makimoto,

I. Kasouka,

S. W. Kim,

M. Ohishi,

K. Nakai,

K. Tobinai,

R. Tanosaki,

S. Mineishi,

Y. Mutou,

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Introduction: Allog-HSCT with a myeloblastic regimen provides a low relapse rate for NHL at the expense of high treatment-related toxicity. Alternatively, allog-HSCT using the RI regimen may be useful because of its lower toxicity. Methods: A total of 24 patients with NHL ineligible for conventional allog-HSCT were treated between May 2000 and Nov 2001. The median age was 51 y (range, 25-61). Fourteen patients had chemotherapeutic disease, 9 relapsed after autograft. The histology of NHL consisted of indolent (n=10) and aggressive NHL (n=14). All the patients received a purine-analog and associating agent based preparative RI regimen with or without ATG and received G-CSF-mobilized blood stem cells from an HLA-matched sibling. Results: All but one patient achieved engraftment with acceptable regimen-related toxicities. Of 19 patients evaluable for chronic GVHD (limited, 2; extensive, 12), 10 of patients developed chronic GVHD (limited, 2; extensive, 12). Tumor regression was observed within several months after transplant and with chemoresistant disease prior to transplantation achieved a CR without any signs of GVHD. With median follow-up of 327 days, 9 of 10 patients (90%) were in CR. Kaplan-Meier estimates for 1-year overall (OS) and progression-free survival (PFS) were 73% and 66%, respectively. Conclusion: The high response rate with low toxicity suggests that HSCT is an effective and safe treatment for high-risk patients with disseminated mantle cell lymphoma (MCL).

High Dose Sequential (HDS) Chemotherapy Regimen As Up-Front Treatment Improves the Outcome of Patients with Disseminated Mantle Cell Lymphoma (MCL).


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Purpose: To evaluate the efficacy of ifosfamide, etoposide, and cisplatin (IEV) chemotherapy followed by High-Dose Chemotherapy (HDC) and ASCT for patients (pts) with diffuse large cell lymphomas (DLCL) refractory or relapsed to conventional chemotherapy. Patients and methods: From 11/91 to 7/2002, 82 pts with DLCL received IEV chemotherapy: ifosfamide 250 mg/m² d-1-3, Etoposide 150mg/m² d-1-3, Meas 3000 mg/m² d-1-2 (d for 21 days for a total of 3 courses). Sicoy pts were in first relapse, 28 of which in early relapse (<12 months from diagnosis) (ER) and 32 in late relapse (>12 months) (LR). Thirteen pts were in second relapse and 9 refractory to induction therapy. Of the 53 pts available for IP1 at first relapse 15/33 had a high-risk (IP1 2-3) and 35/53 had low-risk (IP1 1-2). All pts who achieved a response (PR-CR) to IEV were eligible for intensification with a HDC (BEAC/BEAM) and ASCT. The source of stem cells was bone marrow in the first 26 pts and after 2005 all consecutive pts employed peripheral stem cells, mobilized with G-CSF given at day +5 after the 3rd course of IEV.Thirty-eight (40) (95%) pts collected > 2x10^6 CD34+ cells. Results: Sixty-nine (82) (94%) pts 37/69 (54%) of which relapsed and 69% (66%) refractory achieved a PR-CR after IEV chemotherapy and were considered eligible for intensification with HDC-ASCT. Of 69 eligible pts did not receive HDC-ASCT (one for refusal and four for low performance status after ER). After a median follow-up of 41 months (6-144) the 3-yr OS and EFS for all 82 pts were 40% and 24% respectively. Two (4%) (3%) transplant-related deaths were observed. The 3-yr OS and EFS were respectively 45% vs 0% (p=0.007) and 27% vs 0% (p=0.02) for chemoresistant compared to chemoresistant pts with PR or CR. The OS were 45% vs 52% (p=0.12) and 19% vs 34% (p=0.04) for the 3 yrs OS was 19% vs 38% (p=0.005) and the EFS was 9% vs 13% (p=0.002) respectively in pts with a high or low risk IP1 at relapse. Conclusions: IEV has been active and able to induce a high response rate and allowing to mobilize PBSC in high percentage of pts. Chemoresistant pts, with an early relapse (<12 months from diagnosis) or an high-risk IP1 (2-3) at relapse, showed a poor prognosis and new strategies might be investigated for them.

Conclusions: This observational phase II multicenter study shows that HSCT with PBPC autograft, given as front-line treatment, can improve the outcome of patients with disseminated MCL.

Results: 34 patients (82%) in HDS group compared to 16 (25%) in non-HDS group achieved CR (P=0.0001), 3 (9%) and 34 (48%) PR and the treatment-related mortality was 2% and 3%, respectively. With a follow-up of 31 (HDS group) and 35 months (non HDS group) the clinical outcome seems better in HDS group (4 year OS 63% vs 47%, P=0.06; EFS 46% vs 11%, P=0.0001; FP 47% vs 18%, P<0.0002). Besides bone marrow transplantation versus chemotherapy, respectively. 11/10 pts were in partial or CR. 9 pts achieved a PR-CR after autograft. The histology of NHL consisted of indolent (n=10) and aggressive NHL (n=14). All the patients received a purine-analog and associating agent based preparative RI regimen with or without ATG and received G-CSF-mobilized blood stem cells from an HLA-matched sibling. Results: All but one patient achieved engraftment with acceptable regimen-related toxicities. Of 19 patients evaluable for chronic GVHD, 14 achieved a complete response (CR) and 2 progressed post-transplantation. Fourteen patients developed acute GVHD (grade 1, 3, grade 2-IV, 11), and 14 of the 21 evaluable patients developed chronic GVHD (limited, 2; extensive, 12). Tumor regression was observed within several months after transplant and with chemoresistant disease prior to transplantation achieved a CR without any signs of GVHD. With a median follow-up of 327 days, all 10 patients (100%) were in CR. Kaplan-Meier estimates for 1-year overall (OS) and progression-free survival (PFS) were 73% and 66%, respectively. Comparison between indolent and aggressive lymphomas showed OS of 100% (P=0.20) and PFS was 88% and 50% (P=0.07), respectively. Conclusion: The high response rate with low toxicity suggests that HSCT is an effective and safe treatment for high-risk patients with disseminated mantle cell lymphoma (MCL).
INCIDENCE, CLINICO-PATHOLOGICAL FEATURES, AND PROGNOSTIC FACTORS IN T-CELL LYMPHOMAS: DATA FROM A DANISH POPULATION-BASED LYMPHOMA REGISTRY.
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On behalf of the Danish Lymphoma Group, Lymphoma Project.

Aim: To analyze T-cell malignancies in western Denmark with regard to occurrence, clinicopathological, and prognostic features, treatment response and outcome.

Methods: A total of 5613 cases were registered between 1983 and 2000. Immunophenotyping was available in 4049 patients. Of these, 430 (19.1%) were T-cell malignancies, corresponding to an annual incidence of 0.9/100,000/year. Histological subtypes included T-lymphoblastic (T-LBL) 13%, cutaneous anaplastic large cell (c-ALCL) 3%, peripheral T-cell (PTCL) 60% (including systemic ALCL, angioimmunoblastic, and anaplastic type), and T-cell lymphomas, and low-grade cutaneous T-cell lymphomas 10%. 14% of cases with T-cell phenotype were unclassified. Lymphomatous cases were not registered. Histologically aggressive T-cell subgroups, i.e., c-ALCL, T-LBL, and PTCL, were individually compared with diffuse large B-cell lymphomas (DLBCL, n=1287) in terms of clinical and prognostic features. T-LBL and c-ALCL had the youngest patient populations. c-ALCL cases were more often localized and in a better performance status. T-LBL had the highest frequency of cases with elevated β2M. This feature was found in roughly a third of DLBCL and PTCL cases, but rarely in c-ALCL. PTCL was often associated with B-symptoms. Almost a third of all PTCL cases had an exclusively extranodal presentation. Treatment response and outcome of different subgroups were:

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Complete response (CR)</th>
<th>Relapse rate</th>
<th>Disease free survival (DFS)</th>
<th>Overall survival (OS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T-LBL</td>
<td>72%</td>
<td>28%</td>
<td>41% 30% 17% 25%</td>
<td>51% 43% 29% 38%</td>
</tr>
<tr>
<td>c-ALCL</td>
<td>67%</td>
<td>36%</td>
<td>41% 34% 18% 25%</td>
<td>51% 43% 33% 37%</td>
</tr>
</tbody>
</table>

Conclusions: As expected, c-ALCL was characterized by a high relapse frequency, but favourable survival confirming the non-invasive nature of this entity. In our material, T-LBL had relatively high CR and DFS values. PTCL, as the largest T-cell subgroup, did not differ significantly from DLBCL in terms of CR-rate, but had a similarly higher relapse frequency. It also showed the lowest DFS and OS-values among all the subgroups tested.

HIGH RESPONSE RATE WITH AN INTENSIVE, SHORT-TERM CHEMOTHERAPY PROGRAM FOR ADULTS WITH BURKITT AND BURKITT-LIKE LYMPHOMA.
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Introduction: Burkitt and Burkitt-like NHL are rare diseases that account for 2% to 4% of all NHLs in adults. Effective, but toxic and labor intensive regimes have been developed. We have tested in a consecutive group of 12 patients a very short, intensive and well tolerated chemotherapy program successfully applied in the past to pediatric patients with Burkitt disease (Est J Cancer 5:697-8, 1993).

Patients and Methods: From Dec 1989 to Oct 2001, 17 patients with Burkitt and Burkitt-like NHL were enrolled. The patient chemotherapy schedule was as follows: MOPP: 8/4, median age: 41 yrs (range 22-65); stage II/III/IV: 6/6; B symptoms: 3 pts; bulky disease: 9 pts; LDH: <1000 U/L in 6 pts; ECOG P.S. 0-3/4-5: 9/3. None had CNS involvement and only 1 patient presented hystologic BM involvement. The regimen consisted of: CTX (500 mg/m², day 1-2), MTX (150 mg/Kg, day 8), VP-16 (250 mg/m² q12h, day 14), MTX (250 mg/Kg, day 21), ADM (50 mg/m², day 28), VCR (1.4 mg/m², day 35), HD Ara-C (1000 mg/m² continuous infusion for 4 days with a daily extra dose of 250 mg/m² plus CDDP (20 mg/m²) q12h). Weekly intravenous chemotherapy for six doses was administered. 4 patients received consolidation radiotherapy on the sites of bulky disease despite negative imaging. The median duration of the chemotherapy program was 61 days (range 46-95).

Results: 83% patients entered CR. One toxic death due to pulmonary infection was observed during treatment in one CR. Two patients experienced disease progression during chemotherapy, but were switched to high-dose sequential (HD) chemotherapy supported by PCRRADOP+ cyclophosphamide peripheral blood stem cell (PBSC) transplant. One of the latter patients is in CR after 23 months, and the second died due to PD. DFSOS and EFS were 82%±11% and 78%±19% respectively with a median follow-up of 29 months (range 3-130) from starting therapy. Except for hematological toxicity after HDARA-CDDP, no major side effects were observed.

Conclusions: In spite of the small number of patients reported: i) CR and DFS were very encouraging, and prompt us to extend treatment to a larger group of patients; ii) the results were in keeping with those achieved with the same regimen in the pediatric setting; iii) HDs regimen supported by PCRRADOP+ PBSC transplant showed activity in refractory patients, and should be investigated as salvage therapy.
IMPROVED OUTCOME OF BURKITT’S AND BURKITT-LIKE LYMPHOMA: COMPARISON OF CODOX-M-IVAC AND MEGAVAC CHEMOTHERAPY IN 84 CONSECUTIVE PATIENTS

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Introduction: Burkitt’s (BL) and Burkitt-like (BLL) lymphomas are rapidly progressive neoplasms leading to death within weeks unless the patient is achieving complete remission or tumor burden is minimal. In the mid-1990s several groups – including NCI-US (L. Magrath et al., J Clin Oncol 1996; 14:925) – reported on major improvement in outcome of children and adult patients treated with intensive, sub-myeloablative regimens of high-dose methotrexate combined with fractionated cyclophosphamide and dexamethasone alternating with high-dose cytarabine and ifosfamide and etoposide. The purpose of this study was to extend and validate previously reported data (Blood 2001; 98, Absor 4740) on toxicity and outcome in BLL/BLL patients treated with Magrath protocol (CODOX-M-IVAC) compared to CHOP-like regimens at our institution.

Methods: First 20 patients were treated with CODOX-M-IVAC within the United Kingdom Lymphoma Group trial LV6 (C. Mead, M. Sykes, Proc ASCO 1999; 18, Abstr 29) and subsequent 30 patients were treated identically after the trial closed (n=50). This group was compared with 24 patients treated in 1978-2000 with conventionally dosed regimens MEGAVAC/CHOP.

Results: Three year overall (OS) and progression-free (PFS) survival for patients treated with CODOX-M-IVAC (30% and 27%) was significantly better (p<0.001) than for patients treated with MEGAVAC/CHOP (30% and 27%). Treatment related mortality (TRM) for both regimens was 8% and 12%, respectively. In a multivariate analysis (Cox’s model) treatment method, bulky disease, and platelet score were significant predictors for OS.

Conclusion: Our data confirm excellent results of CODOX-M-IVAC achieved at the NCIC-US and UKRL. Survival of adult patients so treated is improved 2.7 fold compared to conventional therapy at no expense of TRM.

ISOLATED BONE MARROW INVOLVEMENT IN HUMAN IMMUNODEFICIENCY VIRUS-ASSOCIATED HODGKIN LYMPHOMA (HIV-HEL)

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Introduction: HIV-HEL involves the bone marrow (BM) in approximately 50% of cases at diagnosis compared to 10% to 15% in immunocompetent individuals. BM HIV-HEL is usually recognized at staging following HL diagnosis on a lymph node or other tissue but occasionally is the only site of disease. In the latter setting diagnosis can be problematic. In this study six HIV-HEL cases with BM as the only site of disease at diagnosis are described.

Methods: 22 HIV-HEL patients (16 M; 6 F) had positive BM involvement at diagnosis. From this group 16 patients were found to have substantial histological, and/or clinical extramedullary extension at BM involvement. In the remaining 6 BM was the only site of disease at diagnosis.

Results: All six patients were male and presented with fever and peripheral blood cytopenias. Median age was 35 years (range 31-58). Median CD4+ lymphocyte count was 70 cells/mm³. Total body CT scans and all other staging procedures were negative. All patients were treated with chemotherapy (ABVD/COP in five and BEV in one); one patient is currently under treatment. Median survival was 4 months (range 2-118 months); longer survival was achieved in the patients that completed chemotherapy regimens. In all cases of isolated BM HIV-HEL, BM biopsy revealed HL in either nodules (4 cases) or diffuse infiltrates (2 cases). Diagnostic cells were easily identified in all cases, morphologically and immunophenotypically (CD3+, CD20, CD45, CD45R, ALK-1, and CD30). BEV was demonstrated by in situ hybridization in 3 of 3 cases studied. Extramedullary HL did not occur during the course of disease, but two of three patients who died without the completion of chemotherapy: two of them underwent autopsies, one of which showed disseminated HIV-HEL, four months from diagnosis.

Conclusion: Isolated HIV-HEL may be underestimated condition in patients with HIV infection. In HIV-positive patients with unexplained fever and blood cytopenias, BM biopsy should be performed with the aim of assessing for HL, even in the absence of palpable nodal and visceral HL. A rapid diagnosis of isolated BM HIV-HEL could expedite therapy.

HIGH DOSE THERAPY AND AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION IN HIV-ASSOCIATED LYMPHOMA

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Introduction: The recent introduction of highly active antiretroviral therapy (HAART) has allowed the evaluation of aggressive therapeutic approaches in HIV-positive patients (pts) with lymphoma.

Methods: We started a program of peripheral blood stem cell transplantation (PBSCT) after high dose therapy (HDT) in pts with HIV-associated lymphoma (HLvL) refractory or relapsed after intensive chemotherapy (CT). Eligibility included available effective HAART and no active opportunistic infections (OI) or CNS lymphoma.

Results: Up to January 2002, 7 pts entered the study, 4 with HD (two 1st relapse, one 2nd relapse, one refractory) and 3 with NHL (1st relapse). Median age was 36 (31-56), M:F ratio 2/1, median CD4 count 162/mm³ (35-445), disease stage III-II (2) and IV (5) (marrow in 3). Four pts had chronic HIV hepatitis. First-line CT was Stanford V in HD, and CD or CHOP on ACVB in NHL. Median duration of last remission was 5 months (mo) (1-33). Pts received 1-3 courses of second-line standard-dose CT as debulking treatment. After a mean of 3 (2-5) apsensia, a median of 6.85 (4.3-9.3) x 10⁶/kg CD34+ cells were collected, after cyclophosphamide 4 g/m² + G-CSF in 2 or G-CSF supported standard-dose CT in 3 cases. Median CPU-GEMM, CPU-GM and BFU-E were 6 (3-41), 110 (96-307) and 229 (178-432) col/10⁶ cells. Two pts failed to mobilize. Mobilization and collection were safe with only two episodes of FUO. One pt had progressive HD soon after PBSCT collection and died. Four pts underwent HDT with BEAM (CNU 300mg/m², VP16 200mg/m² x 4, Ara-C 200mg/m² x 4, Melphalan 140mg/m²) and PBSCT transplantation. Prompt hematologic recovery was observed in 4/4 pts (PMN>500/mm³ at +10 (8+10) and self-supporting plus-20/mm³ at +16 (11-18)). Treatment-related toxicity included WHO 2-3 oral mucositis in 2 pts, one WHO 2 facial cellulitis, one WHO 2 Cystad minimized colitis and one episode of PUO. HIV viral load remained undetectable in 5 pts, and 1 pt after transplant. Three pts achieved CR and relapse occurred in 1 pt 5 mo after transplant. One pt, with chronic dacromyocoronic disease to second-line CT, died with disease progression 3 mo after transplant. Three of 4 pts are alive, after a median F-up of 9 mo (2-10), 2 disease-free 3 mo after transplant.

Conclusions: Adequate numbers of CD34+ cells can be collected in most HIV-pts even though with advanced lymphoma and after intensive first-line CT. HDT with PBSCT reinfusion is feasible, with rapid hematologic recovery and tolerable treatment-related toxicity. HIV infection does not seem significantly affected by the procedure in pts on HAART.

INFLUENCE OF HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) ON OUTCOME OF AIDS-RELATED NON HODGKIN LYMPHOMA (AR NHL)

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To compare the presentation and prognosis of NHL in AIDS pts before and after the introduction of HAART.

Methods: Retrospective study of 73 cases of AR NHL between 1992 and 2000 from 2 clinical centers. Event-free survival (EFS) and survival were estimated by Kaplan-Meier method and a Cox model was used to evaluate the effect of different variables on survival.

Results: Median manifestation of NHL was 40.8 years. 22 patients (30.1%) had prior AIDS-defining illness. Median CD4 count was 153/mm³. An Ann Arbor III/IV stage was present in 60 pts (82.2%). Extranodal sites (liver, gastrointestinal tract, bone marrow and neuroendocrine system) were present in 35 patients (83.3%). Intermittent or high-grade histology was the most common presentation (56 were classified as diffuse large cell lymphomas and 12 as Burkitt or Burkitt-like lymphomas). Bone marrow and meningeal involvement were present in 13 (17.8%) and 12 (16.5%) pts, respectively. 67 patients were treated by chemotherapy, 36 received CHOP and 26 ACVB. The median survival (MS) of the 73 patients was 8 months. Two groups were identified according to their treatment. The first group (38 patients) had never received HAART and the second (35 patients) received HAART before or at the diagnosis and treatment of the NHL. There has been no change in stage at presentation, presence of B symptoms, performance status, marrow or meningeal involvement, CD4 cell count at diagnosis and chemotherapy regimens between the two groups. The estimated MS of the first and second group were 6.12 and 11.8 months respectively (p=0.03). Using the Cox model it was shown that HAART has an independent significant effect on EFS. No influence on outcomes was found for other variables including age, mode of HD contamination, AIDS, CD4 cell count, Ann Arbor stage, systemic B symptoms, extranodal involvement and chemotherapy regimens.

Conclusion: Survival of subjects with the diagnosis of NHL being on HAART was improved significantly.
9. New Treatments

Susceptibility of Lymphoid Malignancies to Reovirus Therapy

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Reoviruses were shown to have ability to destroy many different types of cancer cells both in vitro and in vivo. Cells derived from brain, breast, colon, ovarian, and prostate tumors, with activated Ras or other elements of Ras pathway, were shown to be susceptible to reovirus infection and subsequent lysis. In this study, we investigated reovirus induced oncology of lymphoid malignancies. A total of 9 lymphoid cell lines and 20 primary human lymphoid malignancies, as well as normal lymphocytes and hematopoietic stem/progenitor cells, were investigated for reovirus susceptibility. In vitro, the cell lines and the primary samples were challenged with reovirus (serotype 3 Dearing) and viral infection was assayed by cytopathic effects, remaining viability, [35S]-methionine labeling for the detection of viral protein synthesis and progeny virus production. In vivo, Burkitt’s lymphoma Raji and Daudi cell lines were grown subcutaneously in SCID/NOD mice and subsequently infected with reovirus intratumorally. We found efficient reovirus infection and lysis in the Burkitt’s lymphoma cell lines Raji and CA45, and diffuse large B-cell lymphomas (OCY-LY1, 2, 8, and 10). In contrast, Burkitt’s lymphoma lines Daudi, Ramos, and ST456 were resistant to reovirus infection. Significant tumor regression was observed in the Raji but not Daudi cells consistent with the in vitro results. Reovirus susceptibility was also detected in 14 out of the 20 or vivo specimens. While the normal lymphocytes or stem/progenitor cells did not show permissiveness to reovirus, viral sensitivity varied amongst the different types of lymphoid malignancies. The data indicates that reovirus may be an effective agent against human lymphoid malignancies.
TREATMENT OF MALIGNANT LYMPHOMA BY MECHANOCHEMICAL MODIFICATION BOZORUCICIN
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Introduction: It is well known that increased responsiveness of drugs is possible due to formation of additional free radicals as a result of their mechnanochemical modification. The paper was aimed at using mechnanochemically modified antineoplastic antibiotic doxorubicin (DR) polychemotherapy for patients with malignant lymphoma.

Methods: Mechnanochemical modification of DR was performed using a microvibratt mill MMVE-0.005 (Ganter). DR at 10 mg was placed into a chamfer with 5 milling spheres. The intensity of administered mechanical energy was 20 Wg. After this the agents was immediately dissolved in 200 ml of 0.9% NaCl and carried polychemotherapy to patients with malignant lymphoma. Polychemotherapy malignant lymphoma was done to scheme ACOPP. For 20 cancer patients (1st group) was carried polychemotherapy with using non-modified DR and for other 20 patients (2nd group) was carried polychemotherapy with using mechnanochemically modified DR.

Results: To carry out into practice polychemotherapy with using mechnanochemically modified DR we observed that full remission of the swelling process at the patients increased at the 20% and also quantity toxic effects, was as we can observe during polychemotherapy and next days after it decreased in the middle at the 28%. Our results testify to the suitability of mechnanochemically modified DR to increase the effectiveness of treatment of patients with malignant lymphoma. The results of treatment of patients with Hodgkin's and non-Hodgkin's lymphomas when using polychemotherapy scheme with mechnanochemically modified DR.

<table>
<thead>
<tr>
<th>Group of patients</th>
<th>Full remission number of patients, (%)</th>
<th>Partial remission number of patients, (%)</th>
<th>Lack of effect number of patients, (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st group</td>
<td>11 (55)</td>
<td>2 (10)</td>
<td>7 (35)</td>
</tr>
<tr>
<td>2nd group</td>
<td>13 (65)</td>
<td>2 (10)</td>
<td>4 (20)</td>
</tr>
</tbody>
</table>

Analysis of the results showed full remission was observed on 33% more among patients treated with mechnanochemically modified doxorubicin than patients treated by official doxorubicin.

Conclusions: The obtained information testifies expediency of conduction technology of mechnanochemical modification of doxorubicin for polychemotherapy of Hodgkin's and non-Hodgkin's disease patients.

NOVEL PENTOSTATIN/EXTRANUCLEAR PHOTOPHORESIS
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Introduction: Retrospective studies of autologous vs allogeneic stem cell transplantation have demonstrated the relevance of a graft-vs-lymphoma effect, but regimen related toxicities have limited the applicability of this approach for high risk patients or those who failed autografts. We developed a novel conditioning regimen for high risk patients which utilizes extranuclear photopheresis (ECP) for host conditioning, continuous infusion pentostatin and reduced dose total body irradiation (TBI) for immunosuppression, and cyclosporine A (CSA) for prevention of acute graft-vs-host disease (GVHD).

We report results in 14 patients with high risk relapsed and refractory NHL.

Methods: Of 14 patients, 5 had Hodgkin’s Disease (HD) and 9 had non-Hodgkin’s lymphomas (NHL) (1 CTCL, 8 B-NHL). Eight patients had progressed after prior autologous transplantation and 5 had received 1 or more prior chemotherapy regimens. The median age was 41, with 5 patients over age 50. Donors were 6/6 matched related in 9 and unrelated in 6. Patients received 2 days of ECP, followed by 8mg/m2 pentostatin by continuous intravenous infusion over 48 hours, followed by 600 cGy TBI and stem cell infusion. Standard GVHD prophylaxis with CSA and MTX was administered.

Results: All patients had full donor engraftment by molecular chimerism on day +60. Acute GVHD was limited to Grade 2 in 4 patients; no Grade 3 or 4 aGVHD. The median follow up was 271 days. All three evaluable patients with HD and 6/8 with NHL are in remission. Four patients have died, 3 from infection, 1 from progressive disease, for an overall survival of 71%.

Conclusion: Our pentostatin/ECP reduced intensity regimen is well-tolerated and results in early full donor chimerism, effective graft-vs-lymphoma effect with no severe acute GVHD, thus providing a reasonable salvage strategy for high risk patients with refractory NHL.

INTRANAVE INFUSION OF ACTIVATED AUTOLOGOUS MACROPHAGES ARMED WITH ANTI-CD20 MONOClonAL ANTIBODIES CAN YIELD SUSTAINED MOLECULAR REMISSION IN CLL.
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Introduction: The duration of treatment responses in stage B or C CLL depends on the level of the minimal residual disease (MRD). Molecular remission in B cell CLL is defined by PCR negativity for the immunoglobulin heavy chain gene rearrangement. Several phase I and II clinical trials of activated autologous macrophages, sometimes armed with monoclonal antibodies against tumor antigens, have given encouraging results in patients with solid tumors (ovary, mesothelioma, bladder).

Methods:We have conducted a phase II study of activated autologous macrophages armed with anti-CD20 antibodies with the aim of reducing MRD in CLL patients with partial or complete responses, but with MRD detectable by immunophenotyping and PCR. The procedure comprised one apheresis session, yielding a mean of 1.2 x 10⁹ mononuclear cells. Culture with a MAK cell processor (Immono-Designed Molecules, Paris) for one week in medium containing GM-CSF yielded a mean of 1.65 x 10⁹ macrophages (MAK). The MAKs were then activated with gamma-interferon for 16 h and resuscitated intravenously after 2 h incubation with 2.5 mg of Rituximab. Each patient was scheduled to undergo this procedure weekly for 6 consecutive weeks. MRD studies by immunophenotyping, standard PCR and chimeric PCR were planned before treatment, every month for 6 months post-treatment, then every three months in responding patients.

Results: Ten patients were included and treated. A total of 8 MAK + anti-CD20 infusions were completed without clinical or biological adverse events. Two of the 9 evaluated patients to date have entered immunophenotypic and molecular remission, currently for 18 and 15 months. The kinetics of these two remissions and their long duration suggest an immune response which is currently studied.

REVERSAL OF FORTUNE: USING A TGF-$
\beta$-RELATED IMMUNE EVASION STRATEGY TO ENHANCE IMMUNITY TO T-MR IMMUNITY.
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Introduction: TGF-$\beta$ is a pleiotropic cytokine that regulates cell growth and differentiation. Tumors may secrete TGF-$\beta$ to inhibit tumor-specific cellular immune responses. The TGF-$\beta$ receptor II mutant (DNR) has dominant -ve effects on TGF-$\beta$ signaling. Therefore, if this mutant renders CTL resistant to TGF-$\beta$ this may have clinical importance in the in vivo survival and function of tumor-specific CTL used as immunotherapy of TGF-$\beta$-secreting tumors such as EBV +ve Hodgkin's lymphoma (HL).

Objectives: Our aim was to determine whether EBV-specific CTL lines can be genetically modified with a dominant -ve TGF-$\beta$ receptor in vitro and whether these CTL become resistant to the inhibitory effects of TGF-$\beta$.

Methods: EBV-CTL were transduced with a retroviral vector expressing the DNR. Cytotoxicity, proliferation and cytokine release assays were performed to compare the effects of exogenous TGF-$\beta$ on DNR-transduced and mock-transduced CTL.

Results: Unlike untransduced or mock-transduced CTL, DNR-transduced CTL were resistant to the anti-proliferative effects of recombinant TGF-$\beta$. TGF-$\beta$ receptor ligation results in phosphorylation of Smad2 and this pathway was disrupted in DNR-transduced CTL confirming blockade of the signal transduction pathway. The decreased cytotoxicity and cytokine release demonstrated by nontransduced CTL in the presence of TGF-$\beta$ was not seen in DNR-transduced-CTL. Importantly, while DNR-transduced-CTL were protected from the negative effects of TGF-$\beta$, long-term expression of this construct had no deleterious effects on the function, phenotype or growth characteristics of the transduced-CTL lines.

Conclusions: The functional persistence of TGF-$\beta$-resistant EBV-CTL may be greater than that of non-transduced CTL in patients with EBV +ve HL. Further, CTL expressing a dominant -ve TGF-$\beta$ type II receptor may have a selective advantage in vivo in patients with TGF-$\beta$-secreting tumors.
THE HISTONE DEACETYLASE INHIBITOR SUBEROXYLANILIDE HYDROXAMIC ACID (SAHA) INDUCES GROWTH ARREST AND APOPTOSIS IN B-CELL MALIGNANCES.
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Histone acetylation plays a crucial role in transcriptional regulation, presumably by modulation of chromatin structure. Transcriptionally silent chromatin is more composed of nucleosomes containing histones with low degree of acetylation on the lysine residues of their N-terminal tails. Acetylation of core nucleosomal histones (HATs) is regulated by the opposing activities of histone acetyltransferases (HATs) and histone deacetylases (HDACs). Acetylation of histone proteins neutralizes the positive charge on lysine residues, thereby permitting unfolding of the associated DNA, access by transcription factors, and consequent changes in gene expression. Hydroxamic acid-based hybrid polar compounds, which inhibit HDACs, induce accumulation of acetylated core nucleosomal histones in cultured cells, and promote differentiation and apoptosis of transformed cells. Because the growth-suppressive potential of these agents appears restricted to transformed cells, HDAC inhibitors represent promising novel anticancer agents, and clinical evaluation of these agents is underway. In this study, we investigated whether suberoylanilide hydroxamic acid-based HDAC inhibitors, has activity against B-cell malignancies, such as Waldenstrom’s macroglobulinemia (WM), diffuse large B-cell lymphoma (DLBCL) and multiple myeloma (MM). SAHA as well as SAHA-resistant cell lines sensitive to SAHA-induced apoptosis and of histone acetylation and proteins, including WM and MM patients. SAHA- and hydroxamic acid-treated B-cells express the cell death and caspase-3, -8 and -9 expression, and their activity in these agents appears restricted to transformed cells. SAHA-induced apoptosis is mediated by caspase-dependent and -independent pathways that are independent of histone acetylation. SAHA-induced apoptosis is mediated by caspase-dependent and -independent pathways that are independent of histone acetylation.
EFFICACY OF SINGLE ADMINISTRATION OF A FIXED DOSE PEGFILGRASTIM (PEGYLATED G-CSF) IN INDUCING NEUTROPHEL COUNT RECOVERY AFTER TREATMENT WITH TOPOTECAN CHEMOTHERAPY IN PATIENTS WITH RELAPSED LYMPHOMA

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Introduction: Pegfilgrastim (PF) is a pegylated form of G-CSF that has a long half-life allowing for a single administration per chemotherapy cycle. In two recent randomized studies in patients with breast carcinoma, a single injection of PF per chemotherapy cycle has been shown to be as effective as daily administration of G-CSF in reducing neutrophil recovery and reducing the incidence of chemotherapy-induced neutropenic infection. In this study, we examined the efficacy of PF after taxol + topotecan chemotherapy in patients with relapsed lymphoma, and compared the results to our previous experience using the same chemotherapy regimen with daily G-CSF support.

Methods: Patients received paclitaxel 200 mg/m² iv on day 1 + topotecan 1 mg/m² iv daily days 1-9. On day 8-10 yrs were given a single fixed dose of PF (6 mg) subcutaneously. WBC and absolute neutrophil counts (ANC) were monitored three times/week. ANC ≥ 1000.

Results: Results from the first 7 enrolled patients (35 pts are planned) are analyzed. Mean pre-treatment WBC/ANC was 7.9/5.19 × 10^9/l. Counts nadired on day 9-10 (WBC 0.9/6, ANC 0.19/6), and recovered by day 11-12 (WBC 2.9/6, ANC 1.9/6). Two patients developed neutropenic fever which was associated with infection in one. Two patients reported grade II bone pain, but no grade III/IV PF-related toxicity was observed.

Conclusions: Our preliminary data suggest that prophylactic use of a single dose per cycle of PF compares favorably with our experience using the same chemotherapy regimen with daily G-CSF support in terms of neutrophil count recovery and the incidence of neutropenic fever. The convenience of a single dose of PF per chemotherapy cycle may improve patients’ compliance and quality of life.

RASBURICASE (R) SIGNIFICANTLY REDUCES URIC ACID (UA) AND CREATININE (C) LEVELS IN PATIENTS WITH BURKITT’S LYMPHOMA (BL) AND B-ALL AT RISK FOR TUMOR LYSIS SYNDROME (TLS)

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Introduction: The incidence of hyperuricemia (HU) and TLS is significant in patients (pts) with BL and B-ALL. The development of acute renal failure (ARF) requiring dialysis may be as high as 25% following TLS with allopurinol therapy (Boyanova et al, JCO 14:122, 1996). Allopurinol (A) inhibits xanthine oxidase preventing UA formation but does not breakdown preformed UA or existing xanthine or hypoxanthine. R is a recombinant urate oxidase which breaks down uric acid to allantoin which is 5 times more soluable than UA. We have previously demonstrated R to be significantly superior to A in reducing exposure to UA in pts with hematological malignancies at risk for TLS (Goldman-Cairo et al, Blood 97:1998, 2001).

Methods: We retrospectively reviewed the efficacy of R to both treat and prevent HU in 24 pts with BL and B-ALL. Pts received R (0.15-0.20 mg/kg) IV over 30 min for 3-7 days. UA response (UA-R) was defined as reduction or maintenance of UA to <75 mg/dl (<4.5 mg/dl <3 yrs) within 48 hrs and control of HU under treatment. Creatinine (C) was expressed as % creatinine (adjusting for age and gender). Chemotherapy was started within 48 hrs (hrs) of first dose of R.

Results: 28 pts, 22 stage IVB/IV BL, 6 B-ALL, age 9 yrs (1-17), 23.5±5.6, LDH HU (N=12), 7.47 IU/ml (38.8-10.434), LDH norm-HU (N=16) 1407 IU/ml (326-337), were evaluated. Initial mean UA in HU was 14.3 (9.4-30.3) mg/dl and decreased within 24 hrs to 2.3 (0.7-7.1) mg/dl, (p<0.001) and in non-HU initial mean UA was 5.1 (3.3-7.5) mg/dl and decreased to 24 hrs to 1.4 (0.5-4.9) mg/dl (p<0.001). The UA-R rates were 89% (95%CI: 77-100%) and 93% (95%CI: 72-100%) in the HU and non-HU groups respectively. Furthermore, 8% initially in HU subgroup was 161% and decreased to 100% (p=0.044) and in non-HU subgroup was 100% and decreased to 80% (p<0.001) by day 3 after R dose in pts with BL and B-ALL. There was no incidence of ARF or/and dialysis.

Conclusions: These results demonstrate that R both therapeutically and prophylactically significantly reduces UA and maintains UA control after induction of chemotherapy in pts with BL and B-ALL. In addition pts had a significant decline in their creatinine levels reflecting improved renal function and no incidence of dialysis.

PEGFILGRASTIM MINIMIZES HEMATOLOGIC TOXICITY AND DOSES-SSENSE CHOP-R

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INTRODUCTION: Relative dose intensity (RDI) affects outcome in aggressive NHL; efforts to improve efficacy include administration of chemotherapy in 14-day cycles (dose-dense therapy). Dose-dense CHOP can be safely delivered with pegfilgrastim support to NHL patients of all ages, including the elderly (ASC0 2000 #49). The addition of rituximab (R) to CHOP (CHOP-R) may significantly improve survival in aggressive NHL. Pegfilgrastim allows for once-per-cycle corticosteroid-stimulating factor administration. The feasibility of 14-day CHOP-R with pegfilgrastim is under investigation in this phase II trial. The primary endpoint of the final analysis will be the incidence of grade 4 neutropenia over 6 cycles. METHODS: Eligible patients with untreated intermediate, high-grade, or previously treated low-grade NHL receive dose-dense CHOP-R (day 1 R, day 3 “standard dose” CHOP, day 4 single-dose per cycle pegfilgrastim [6-mg fixed dose]) for up to 8 cycles. Planned enrollment is 30 patients. RESULTS: Reported herein are the results of a planned interim safety analysis of the first 6 patients enrolled. To date a total of 25 cycles of treatment have been administered, with only 1 dose delay (1 week) due to grade 1 diarrhea. No instances of grade 4, or febrile neutropenia have been encountered. One patient has required a packed red blood cell transfusion for grade 3 anemia. No instances of grade 4 thrombocytopenia have been encountered. All patients have achieved at least partial response. CONCLUSION: The preliminary data suggest that CHOP-R with pegfilgrastim support can be safely and effectively administered every 2 weeks for at least 3 cycles. In those patients treated with more than 3 cycles of therapy (to date: 6 cycles) this protective effect has persisted without deviation. No unexpected toxicities or adverse events have been encountered, nor have any instances of grade 4, or febrile neutropenia, yet been encountered at this early point in the study. Accrual to the trial continues; updated toxicity and efficacy data will be presented.

OBSERVED/PREDICTED (OP) SERUM ERYTHROPOIETIN (sEPO) RATIO AND PLATELET COUNT ARE IMPORTANT PREDICTORS OF RESPONSE TO EPOETIN BETA IN PATIENTS WITH LYMPHOID MALIGNANCIES

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Introduction: Anemia is very common in patients with lymphoid malignancies and can reduce patients’ quality of life and possibly the effectiveness of anti-cancer therapies. Correction of anemia with epoetin can be achieved in 60–70% of patients with lymphoid malignancies. This large, open-label study evaluated clinical parameters that will allow for identification of patients who can be expected to respond to epoetin therapy.

Methods: Epoetin beta (Neorecormon®): 200–900 IU/kg/wk sc for 24 weeks was administered to anemic patients with lymphoid malignancies (Neutrophilin [fHb] >12 g/dl, maintained for 4 weeks without transfusion following a 4-wk transfusion-free period) was measured every 4 wk. Platelet counts (PC) and sEPO levels were measured at baseline and every 4 and 8 wk, respectively. RESULTS: The OP ratio (ratio of observed sEPO levels at baseline to levels predicted by the degree of anemia) was predictive of response to epoetin beta; patients with an OP ratio >0.8, indicating a relative sEPO deficiency, had a response rate (RR) of 64.7% after 24 wk vs 41.3% for patients with an OP ratio ≤0.8 (P<0.001). Baseline PC also predicted response; RR was 58.8% for patients with PC >100 < 10^4/L vs 38.6% for patients with PC ≤100 < 10^4/L (P=0.001). These two factors combined gave a more powerful prediction of response: patients with an OP ratio <0.8 and PC ≥100 < 10^4/L had a RR of 76% vs 37% for patients with an OP ratio >0.8 and PC ≤100 < 10^4/L. Duration since diagnosis of malignancy is a further prognostic factor, with the likelihood of response declining in patients with a longer history of disease.

Conclusions: Indices of relative sEPO deficiency (OP ratio) and bone marrow function (PC can be used, particularly in combination, as predictors of response to epoetin beta in patients with lymphoid malignancies.
608

EPOETIN BETA (NEORECOMB) IMPROVES QUALITY OF LIFE (QoL) AND PREVENTS ANEMIA AND DECREASES REQUIREMENT FOR RBC TRANSFUSION IN PATIENTS WITH SOLID AND HAEMATOLOGICAL MALIGNANCIES

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Introduction: Most patients with malignant disease are anaemic or become anaemic during treatment and experience a significant reduction in QoL (associated with fatigue, social withdrawal and depression). This open-label, prospective, randomised trial investigated the effect of epoetin beta, an effective and well-tolerated treatment for cancer-related anaemia, on QoL in patients with solid and haematological malignancies in comparison to standard care.

Methods: Anaemic patients (haemoglobin [Hb] <11 g/dL; n=262) with haematological (n=144) or solid malignancies (n=118) received epoetin beta (150–300 IU/kg three times weekly) or standard care (including blood transfusions) for 12 weeks. Endpoints included response to therapy (Hb >2 g/dL increase in Hb after the initial 4 weeks of therapy without need of transfusion). QoL was assessed using the SF-36 physical component summary score (SF-36 PCS), the FACT-An and FACT-F subscales of the FACT-An questionnaire and a visual analogue scale (VAS).

Results: The proportion of patients responding to therapy (47 vs 13%; P<0.001) and the median increase in Hb (2.1 vs 0.9 g/dL; P<0.001) were significantly greater in the epoetin beta compared to the standard care group. A serum erythropoietin level of <50 mIU/ml was significantly predictive of response (OR: 2.496, 95% CI: 1.21–5.13). In the epoetin beta group baseline-to-fatal visit median changes in QoL for SF-36 PCS (2.1 vs 0.7 points; P<0.05), FACT-F (3.0 vs 1.0 points; P<0.05) and VAS (10.0 vs 1.0 points; P<0.01) were significantly greater than in the standard care group. Changes in the FACT-An subscale tended to be greater in the epoetin beta group (1.0 vs 0 points; P=0.076). Increases in the SF-36 PCS and FACT-F PCS scores correlated significantly with Hb response (P<0.01).

Conclusion: Compared with standard care, epoetin beta reverses anaemia and promotes significant Hb-associated increases in QoL in anaemic patients with solid and haematological malignancies.

610

DARBEPOETIN ALFA ALLEViates ANEMIA IN PATIENTS WITH LYMPHOPROLIFERATIVE MALIGNANCIES AND SOLID TUMORS

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Introduction: Determining the optimal darbeopetin alfa (Anarase™) dose in major subpopulations such as lymphoproliferative disorders (lymphoma) and solid tumors may provide more effective management of patients (pts) with anaemia. This report compares the dose-response of darbeopetin alfa in these two populations.

Methods: Two similarly-designed dose-finding studies were conducted in anemic pts (hemoglobin <10.0 g/dL) with lymphoma (n=50) or solid tumors (n=124) who were receiving chemotherapy. Pts who had received recombinant human erythropoetin (rHuEPO) therapy within 8 weeks (wks) or >2 red blood cell transfusions (RBCs) within 4 wks before the study. Darbeopetin alfa 1.25 g and 4.5 g/kg was administered subcutaneously once weekly for up to 12 wks in both studies. Data for all doses will be presented.

Results: The adverse event profile of darbeopetin alfa was similar between tumor types and was consistent with that expected for cancer pts receiving chemotherapy. Equivalent doses of darbeopetin alfa administered to pts in both disease settings result in similar effects on multiple parameters including high blood pressure (12.5 g), lymphocytosis and neutropenia (12.5 g). Patients with solid malignancies required a dose of 1.25 g/kg to achieve the target Hb of 12 g/dL, whereas lymphoma pts required a dose of 4.5 g/kg to achieve the target Hb of 12 g/dL. The hemoglobin and reticulocyte responses were comparable in both populations.

Conclusion: Comparability of the results between anemic pts with solid tumors or lymphoproliferative malignancies treated with darbeopetin alfa indicates that darbeopetin alfa is safe and effectively reverses chemotherapy-induced anaemia in both treatment settings, with no apparent difference in the dose-response relationship.

611

THE SIGNIFICANCE OF ADDITION OF DG3 IMMUNOTHERAPY TO ROUTINE TREATMENT OF MALIGNANT LYMPHOMA

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Introduction: The aim of this work is to study the possibility of addition of DG3 immunotherapy to routine treatment of malignant lymphoma to increase the therapeutic effect.

Methods: DG3 scarification is used and the treatment effect is monitored by dynamic change of OT skin test reactivity and clinical disease course. Results: Both malignant lymphoma patients (n=207) and non-tumor subjects (n=25) showed a broad distribution spectrum of reaction to different OT dilution, but the clinical tumor patients showed the marked tendency of decreased reaction and the treated patients in their disease free life showed the recovery of OT skin test reactivity to the normal level of non-tumor subjects. Most successfully treated patients demonstrated the recovery and enhanced OT skin test reactivity even after the chemo-radiotherapy, and markedly affected by the addition of DG3 treatment. In the long-term follow-up patients, it is demonstrated a close relationship of the immunostatus and the suppression or progression of the disease, and the effect of immune reactivation of the DG3. Conclusion: It is reasonable to add DG3 to routine treatment of malignant lymphoma and to use OT skin test for monitoring the therapeutic response and predicting prognosis.