
Summary: Patients with Hodgkin's disease (HD) which is refractory to first line chemotherapy, those who relapse rapidly or who have multiple relapses have a very poor prognosis. With the increasing use of hybrid chemotherapy schedules these patients will have already been exposed to many of the drugs active in HD so it is important to develop salvage schedules that are novel, relatively non-toxic and demonstrate activity in this group of patients. We report the use of a continuous high dose infusion of ifosfamide at a dose of 9g/m² over 3 days in combination with etoposide 200mg/m² given over 2 hours on days 1-3 and eribulin 50ng/m² on day 1; only MESNA cover was given. The aim was to give 3 courses at 21 day intervals followed by autologous stem cell transplantation with either BEAM or Melphalan/VP16 conditioning. Forty six patients (28M:18F) with a median age of 28 years (range 13-45) were treated. Overall 38 out of 46 (83%) with histological confirmed disease responded to treatment, with 17 achieving complete remission and 11 a good partial remission of whom 21 proceeded to autologous bone marrow/stem cell transplantation. In total, 23 patients are alive and in continuous remission with a follow up of between 12 and 61 months. Haematological toxicity, particularly neutropenia (WHO grade IV), was observed in all cases but improved over the 3 courses of treatment in the majority of patients. Non-haematological toxicity was not a major problem. No significant cardiac, hepatic, renal, pulmonary or central nervous system toxicity was observed and there were no deaths on treatment. One patient, treated in second relapse, died of secondary acute myeloid leukemia 46 months after treatment whilst her HD was still in remission.

A DOSE-FINDING STUDY FOR LENORGASTIM IN PBSC MOBILISATION IN PATIENTS WITH NON-HODGKIN’S LYMPHOMA


The use of autologous PBSC rescue after high dose therapy has almost totally replaced the use of ABMT. G-CSF is commonly used to mobilise PBSC, however to date no conclusive dose-finding study has been performed. We investigated the optimum dose of glycosylated G-CSF (lenogastim) for PBSC mobilisation in 43 previously-untreanted patients with aggressive NHL scheduled to receive ablative chemotherapy. Patients received six courses of biweekly CHOP supported with lenogastim before conditioning and PBSC apheresis was started from the 3rd course until enough PBSC were collected. Lenogastim was administered daily from day 3 until the day of the last apheresis, in each course. The optimum dose was determined based on mobilisation and safety in the 1st part of the study at a daily dose of 2.5 and 10 μg/kg SC for 8 patients in each dose. The harvested number of CD34+ cells was higher in the 5 μg/kg than in the 2 μg/kg group (p<0.001), and sufficient PBSCs (≥2x10^6 CD34+ kg) were collected with one apheresis in the 5 μg/kg dose group which indicated that the optimum dose was 5 μg/kg. This led us to investigate further the dose of 5 μg/kg in an additional 19 patients in the later phase. 13 out of 16 evaluable patients (81%) attained a sufficient PBSC collection level with one apheresis. No clinically significant adverse drug reactions were observed and rapid haematological recovery was attained in all autografted patients. We therefore conclude that 5 μg/kg is the optimum dose for lenogastim in this setting.
EFFICACY AND TOXICITY OF HIGH-DOSE BUSULFAN/CYCLOPHOSPHAMIDE (BU/CY) AND AUTologous BLOOD STEM CELL TRANSPLANTATION (ABSC) IN PATIENTS WITH RELAPSED LYMPHOMA


Introduction: High dose chemotherapy and ABSC was shown to be effective in relapsed lymphoma. The best conditioning regimen and the optimal time of such a therapy is still at question. We included 66 patients with relapsed lymphoma pretreated with combination chemotherapy (2 - 4 regimen) and proven chemosensitivity to salvage therapy in a protocol of BuCy and ABSC.

Characteristics of pts: 37 males, 24 females, age 19-68 (median 49 years), among these 18 CR/RCC, 15 CB, 9 CC, 4 CLL, 3 lymphoblastic T-cell,2 immunocyto, 2 immunoblastic, each with Burkitt-, splenocytic, angio-immunoblastic, large cell-lymphocytic, Carlenens-lymphoma, 8 with Hodgkin’s disease .

Methods: Bu was given at a dose of 1 mg/kg every hours for 4 days orally followed by iv. 60 mg/kg for 2 d Cy. ABSC was performed 48 hours after the last dose of Cy. rG-CSF was given s.c. until engraftment, low-dose-heparin c.i. during hospitalisation and s.c. for one month prior for prevention of hepcite veno-occlusive disease (VOD).

Results: Toxicity was moderate. 48 pts had infectious complications, i.e. ancierticotic infection was marked for 6 days at mean (range 0 to 26). 42% of pts suffered from mucositis WHO/IIV, 32% from nausea/vomiting WHO/III, 18% from diarhoea WHO/II. Only 1 pt developed minor hepatic VOD. 2 pts suffered from manifested hepatitis B with lethal outcome in both (1 pt had also progressive lymphoma); 3 pts developed secondary malignancies (2 acute leukemia with lethal outcome, 1 lung cancer, alive). There was no therapy related early death. Follow up ranges from 3-56 months (median 12.5). The 3-year Kaplan-Meier estimates of overall survival for low grade lymphoma were 76% and 30% for high-grade B-cell-lymphoma, the corresponding estimates of event-free survival were 45% and 10%.

Conclusions: High-dose BuCy with ABSC is a well-tolerated, safe and effective regimen in relapsed lymphoma patients. BuCy could be investigated in randomized trials vs total body irradiation containing or alternative chemotherapy combination regimens.

SUCCESSFUL TREATMENT WITH HIGH DOSE THERAPY IN AGGRESSIVE NON-HODGKIN’S LYMPHOMA WITH MASSIVE BONE MARROW INVOLVEMENT: A REPORT OF THREE CASES

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Introduction: High dose therapy (HDT) supported by peripheral blood stem cell transplantation (PBSCT) is an accepted treatment strategy for patients with aggressive grade lymphomas. We report 3 cases of NHL with massive bone marrow involvement successfully treated with HDT/PBSCT.

Case Report: Characteristics of the 3 pts are shown in Table. All of them had an aggressive B-cell lymphoma with massive BM involvement. They were treated with 3 courses of CHOP-ABVP therapy and achieved CR. PBCSs were collected during the hematological recovery phase in the 3rd course of CHOP-ABVP. The pts went through HDT/PBSCT in 3 months after CHOP-ABVP. HDT consisted of TBI 2Gy x 2 on d 8-7, 6, VP16 150mg/m2 on d 5 and TbiPEPA 200mg/m2 on d 1, 2, 3. Non-purged autologous PBS (3.2-4.9 x 10^6 CD34-cells/kg) were infused on d 0. Hematological recovery was seen on d+10-13 and toxicity was tolerable. All pts were in continuous CR with the follow up time of 41, 25 and 10 months, respectively.

Table: Patients’ Characteristics

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# No. of extranodal sites

Conclusion: CHOP-ABVP therapy and upfront HDT/PBSCT will induce the remission of bulky mass involvement in the pts with massive BM involvement.

HIGH-DOSE CHEMOTHERAPY AND PBPC AUTOGRAPHING INDUCE DURABLE MOLECULAR REMISsions IN FOLLICULAR, BUT NOT IN SMALL LYMPHOCYTIC AND MANTLE CELL LYMPHOCYMAS

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Introduction: We have investigated the role of high-dose (HD) chemotherapy in patients with B-cell low-grade lymphomas at diagnosis. Forty-eight patients with advanced stage B-cell non-Hodgkin’s lymphomas (NHL) (9 small lymphocytic [SLL], 28 follicular/transformed [FL], and 11 mantle cell lymphomas [MCL]) were enrolled in a HD chemotherapy program including a final autografting phase. The program consisted of 2 APO courses (adriamycin-containing regimen), 1 or 2 DHAP, etoposide 2.5 g/m², methotrexate 8 g/m², 40 days interval with high-dose demethasone (25 mg/m²), cyclophosphamide 2.5 g/m², and finally mitoxantrone 60 mg/m² and melphalan 180 mg/m² followed by autografting.

Methods: Minimal residual disease (MRD) has been evaluated on peripheral blood progenitor cells (PBPC), bone marrow (BM) cell harvests, and after autografting, MRD was assessed by PCR, using the 1c-2, 1d-2 or Igh gene rearrangements as tumor cell markers.

Results: In 46 of 48 patients (93%), a molecular marker was available (3 based on bcl-1, 21 on bcl-2 translocations, and 16 on Igh genes). One hundred ten PBPC and 38 BM harvests have been analysed so far. In 20 of 40 patients, lymphoma cells were not detected in some PBPC and/or BM cell harvests: 1 of 7 SLL (14%), 18 of 24 FL (69%), and 11 of 11 MCL (9%). It is noteworthy that after autografting, most of the patients with PCR-negative harvests maintained a durable clinical and molecular response. Fisher’s exact test showed a significantly higher relapse rate in PCR-positive patients.

Conclusion: HD chemotherapy was able to provide clinical and molecular remissions in a sizeable fraction of FL, but novel treatment modalities are required for SLL and MCL. A combined approach of monoclonal antibody therapy (rituximab) plus HD chemotherapy has been planned.

CHOP-ABVP therapy and upfront autologous peripheral blood stem cell transplantation (PBSCT) in the treatment of aggressive non-Hodgkin's lymphoma (NHL): A pilot study

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High dose therapy (HDT) supported by PBSCT in the first-line treatment (upfront HDT/PBSCT) is one of the challenging treatment strategies for high-risk NHL, but its usefulness remains under debate. We made a clinical trial of intensive induction chemotherapy followed by upfront HDT/PBSCT for the pts with aggressive NHL. Patients and methods: Between June 1994 and May/1998, 30 pts of age under 65, with PS 0-4 and well-responded organ function, with stage II-IV, were treated with 3 courses of CHOP-ABVP therapy (Table). Nine (9) pts who had advanced including massive bone marrow involvement, with elevated LDH level and/or bulky disease underwent upfront HDT/PBSCT. HDT consisted of TBI (fractionated, 12 Gy), etoposide (1500 mg/m²) and thiotepa (600 mg/m²) in the majority of the pts.

Results: Twenty-six (87%) of the 30 pts achieved CR by CHOP-ABVP. Failure-free survival (FFS) was 51% at the 19 months of median follow up time for the 21 pts who had not received HDT/PBSCT. Eight (88%) of the 9 pts treated by HDT/PBSCT were in FFS at 28 months of median follow-up time. There were pts with massive bone marrow involvement included in the long-term relapse-free survivors. Acute toxicity was relatively mild with no treatment-related death.

Conclusion: CHOP-ABVP therapy produced a high CR rate, but insufficient FFS without HDT/PBSCT followed by CHOP-ABVP and upfront HDT/PBSCT showed a promising long-term FFS, even in the pts with massive bone marrow involvement.

8. High Dose Therapy
DOUBLE AUTOTRANSPLANT FOR HIGH-RISK LYMPHOMA: A FEASIBILITY STUDY.

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Introduction: Double autotransplant (DAT) has been recently proposed to improve results in high-risk lymphomas. However, the DAT procedure may lead to an increased risk of toxic effects related to conditioning regimens. We present here the toxic effects observed in six patients (pts) included in a feasibility study realized at our institutions.

Patients: Six pts with aggressive lymphomas (6 NHL in PR after conventional therapy; n = 4, NHL in second CR; n = 1 and refractory HD; n = 1) were studied.

The median delay between the 1st and 2nd transplant was 83 days (range 31-118).

The conditioning regimen for first transplant was BEAC (n=3), BEAM (n=2), or NCBV (n=1). Melphalan (140 mg/m² x 1 d) was associated with carboplatin (400 mg/m² x 2 d) and TBI for the NHL pts and with Busulfan (1 mg/kg x 4 d) and Ara-C (400 mg/m² x 2 d) for HD patient. The mean number of CD 34+ cells infused for the second transplant was 13.1 (range 5.3-63.2). Prophylactic bruxism was used in all patients for the second transplant.

Results: The mean time for plateau (>/= 20 x 10^9/L) and PNN recovery (>0.5 x 10^9/L) were 20 (range 12-120) and 13 days (range 4-19) following the second transplant. Mucositis was observed in all pts (grade 2; n = 3, grade 3; n = 2, grade 4; n = 1). Documented infectious complications consisted of Staphylococcus Aureus septicaemia (n = 1), Aspergillus Fumigatus pneumonia (n = 1), and disseminated candidosis (n = 1). Three of these infections were successfully treated. One case of herpes zoster virus infection and one case of necrotising enteritis leading to definitive unilateral colostomy was observed. One patient presented cerebral thrombophlebitis on day 11 post second transplant, which fully recovered. One patient developed acute periarteritis with temporocranial, requiring pericardiocentesis, and died 3 days later from sepsis. Asymptomatic transient alteration of kidney function (n = 2) and elevation of liver enzymes (n = 2) were observed. No case of severe vaso-occlusive disease was diagnosed.

Conclusions: These results show that severe toxic events can occur frequently following DAT. This significant morbidity of the procedure must be taken into account in the design of future prospective trials on DAT.

THE TUMOR LOAD OF PBSC HARVESTS PREDICTS THE OUTCOME AFTER B-CELL PURGED AUTOTRANSPLANTATION IN LOW-GRADE LYMPHOMA.


Introduction: Purging of autologous transplants in low-grade lymphomas in conjunction with high-dose therapy is an option because of the high rate and extent of tumor contamination. We examined immunomagnetic B-cell purging of PBSC autografts and tried to determine the variables predicting the outcome.

Methods: As treatment and for blood stem cell mobilisation 18 patients with a relapsed B-cell non-Hodgkin's lymphoma (12 CBCLC, 1 CC, 4 PLL, 1 immunocytioma) 7 female, 5 male, median age 51 years, range 34-62 received IVI chemotherapy. G-CSF (or GM-CSF) for 5 days/week following 3 days rest. PBSC autografts were purged (MaxSep, Baxter) using a panel of 5 different mouse monoclonal antibodies against B-cell antigens (CD19, CD20, CD22, CD23 and CD27) with 2 magnetic bead separation cycles. Myeloblastic chemotherapy consisted of oral busulphan 16 mg/kg and intravenous cyclophosphamide 120 mg/kg. All autografts before and after purging as well as the removed B-cell lymphoma cell fractions were analysed with consent CD3,CD20,CD19 and Gysen analysis for the presence of monoclonal cell populations, which was completed by light-chain restriction analysis in PACS.

Results: In 12/18 cases monoclonal cells were detected and in 7/18 cases still after purging. These results related to the tumor load of PBSC autografts. In 7 PCR-positive cases after purging, a median of 1.5x10⁶ (7.4x10⁶ - 6.5x10⁶) lymphoma cells were detected from the autografts by purging compared with 6.8x10⁶ (1.8x10⁶ - 1x10⁶) lymphoma cells in 5 PCR-negative cases after purging where monoclonal cells had been detected before (p=0.0045). The tumor load of PBSC autografts was determined with PCR and serial DNA dilutions from samples of the complete tumor concentrates which immunomagnetic B-cell purging produced.

Conclusions: The tumor load of PBSC autografts predicts the PCR-status after B-cell purging and the clinical outcome after high-dose therapy. Around 5x10⁶ lymphoma cells in the autograft might constitute a clinically relevant threshold.
Autologous stem cell transplantation for 46 patients with Folicular NHL

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A total of 46 patients have undergone autologous stem cell transplantation for Folicular NHL in 2 transplant centres in the UK since 1992. The median age of the patients at transplant was 46 years (29-58) and 31 of the 46 patients were transplanted with CD34+ selected peripheral blood stem cells. At transplant, patients were in PR (22/39 patients), 2CR (9/39 patients), 3CR (4/39), 1CR (3/39) and 1 progressive disease. All patients except 3 were transplanted following first or subsequent relapses or following a failure to achieve a first CR. The median number of previous chemotherapy regimens was 2. The median CD34 dose was 3.8 x 10^6/kg (range 0.8-27.3) for unpurged grafts (n=15) and 1.79 x 10^6/kg (range 0.4-7.6) for purged grafts (n=26). Four patients failed to achieve CR post transplant and 13 other patients have relapsed at a median of 9 months post transplant. There have been 9 deaths at a median of 13 months post transplant, 4 due to transformation to high grade NHL, 3 from relapse of follicular NHL, 1 sepsis and 1 gastric perforation but only the two deaths in the first 120 days (rapid relapse, gastric perforation). At a median follow up of 22 months, 37 patients are alive with 27 patients remaining in CR and a further 3 patients in a subsequent CR following relapse. We have previously reported the results of conventional PCR monitoring of this group and it will be updated using real-time automated PCR.

HIGH-DOSE SEQUENTIAL CHEMOTHERAPY AND AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANTATION (PBSCT) IN MULTIPLE MYELOMA (MM): TOXICITY AND EFFICACY

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High-dose chemotherapy (HD-CT) and PBSCCT has been shown to improve prognosis in MM. We investigated the toxicity and efficacy of sequentially administered high-dose chemotherapy in patients (pt.) with MM. EL. 5 female, 10 male, median age 51 years (range 35-62). 4 pts. pretreated, IGG (n=8), IGA (n=3), Bence Jone (BJ) (n=3), plasma cell leukaemia (PCl) (n=1). The treatment consisted of 5 phases (P1-5) beginning with (P1) dexamethasone (40mg orally days 1-4), 2-3 cycles every 2 weeks (P2), (P3) cyclophosphamide (400mg i.v.) followed by collection of PBSC, (P3) mitoxantrone (45mg/m2 i.v.) with vincristin (2mg i.v. days 1+8), (P4) etoposide (25mg/m2 i.v). and (P5) melphalan (200mg/m2 i.v.) with CD34+ selected PBSC. A median of 8.1 x 10^6/kg CD34+ selected cells were retransfused (range 3.3-10.6). G-CSF was given during phases 2-5, until recovery of the neutrophils (> 5 x 10^9/L). Response: CR: disappearance of monoclonal gammapathy (MG) in serum and urine, PR: >75% decrease of MG in serum, >90% of BJ proemina). After P1: CR 0/15, PR 8/15, NC 8/15, PD 1/15. Before myeloablative CT (after P4): CR 1/15, PR 8/15, NC 6/15. After P5: CR 5/15, PR 7/15, NC 3/15.

Toxicity (P2-5)

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Results: Two of 9 pts (1 CR1 and 1 CR2) effectively mobilized with regimen A and 7 (3 CR1, 4 CR2) of 9 with regimen B. The median number (range) of CD34+ x 10^6/kg cells before positive selection in these cases was 4.67 (3.3-22.7). Malignant cells were undetectable after the first selection in 3/9 cases (2 CR1, 1 CR2) and after the CD19+ depletion in one additional patient (ML). By contrast, PCR results were for malignant cells in the final product in 5/9 instances. Seven of the nine pts with successful mobilizations have been autografted with a median number of 2.64 (1.54-9.5) CD34+ x 10^5/kg cells. Haematological recovery has been slow in most cases, with one patient experiencing secondary graft failure. One patient (ML) died from pneumonia on month 9 after transplant whilst in clinical and molecular remission. The remaining 6 pts are alive without clinical evidence of disease. Posttransplant PCR studies have been persistently negative in 3 of these 6 cases. Further patient accrual and long-term follow-up are necessary to define the impact of this approach on the final outcome of the patients.


Introduction: Treatment options for lymphoma patients progressing after HD chemotherapy with autologous stem cell transplantation are limited. There is lack of data describing outcome of these patients and there is no standard therapeutic schedule for such a situation.

Patients and methods: We retrospectively reviewed 68 lymphoma patients (46 HL, 22 NHL) treated with ASCT from January 95 to September 98. 28 of them (17 HL, 11 NHL) relapsed or progressed after ASCT. Fourteen of 17 HL and 8 of 11 NHL patients obtained salvage chemo- and/or radiotherapy (including second transplantation in 3 HL patients).

Results: Median time to progression after transplantation was 3 month (range 1-28) in HL and 7 month (range 1-25) in relapsed NHL patients. Seven (41%) relapsed patients with HL are still alive, 3 of them are disease free. Thirty (27%) of relapsed NHL patients are alive and 2 of them are in CR. The median overall survival from progression was 6 month in both HL and NHL patients. Survival after progression or relapse depends probably upon its extent and upon the time from ASCT. Tolerance of salvage treatment was acceptable.

Conclusion: Treatment of relapsing lymphoma after transplantation is possible. More data and clinical studies are need to determine the optimal strategy of salvage therapy.

CD34+CD19+ POSITIVE/NEGATIVE SELECTION FOR AUTOLOGOUS TRANSPLANTATION IN B-LINEAGE CHRONIC LYMPHOID MALIGNANCIES


Introduction: Between July 1997 and December 1998, 7 patients (pts) with chronic lymphocytic leukemia (CLL), 8 with follicular lymphoma (FL) and 3 with mantle-cell lymphoma (MCL) were included in this study to assess the feasibility and efficacy of CD34+ cell selection followed by CD19+ depletion to eliminate tumor contamination in peripheral blood stem cell grafts. Chemoresistant pts and those without a molecular marker of disease, studied by PCR for t(14;14), t(11;14) or Ig rearrangement, were excluded.

Methods: Mobilization regimen was fludarabine, etoposide and G-CSF (regimen A) in 9 cases or cyclophosphamide (CY) plus G-CSF in 9 (regimen B). If >3 x 10^5/kg CD34+ cells were collected in two apheresis, positive/negative selection was performed using the Isolex and MaxSnc systems. All pts were conditioned with CY and TBI.

Results: Two of 9 pts (1 CLL, and 1 MCL) effectively mobilized with regimen A and 7 (3 CLL, 4 FL) of 9 with regimen B. The median number (range) of CD34+ x 10^6/kg cells before positive selection in these cases was 4.67 (3.3-22.7). Malignant cells were undetectable after the first selection in 3/9 cases (2 CLL, 1 FL) and after the CD19+ depletion in one additional patient (MCL). By contrast, PCR results were for malignant cells in the final product in 5/9 instances. Seven of the nine pts with successful mobilizations have been autografted with a median number of 2.64 (1.54-9.5) CD34+ x 10^5/kg cells. Haematological recovery has been slow in most cases, with one patient experiencing secondary graft failure. One patient (ML) died from pneumonia on month 9 after transplant whilst in clinical and molecular remission. The remaining 6 pts are alive without clinical evidence of disease. Posttransplant PCR studies have been persistently negative in 3 of these 6 cases. Further patient accrual and long-term follow-up are necessary to define the impact of this approach on the final outcome of the patients.
HIGH PURITY AND COLLECTION EFFICIENCY OF PERIPHERAL BLOOD CD34+ HEMATOPOIETIC STEM CELLS AFTER MOBILIZATION BY IMMUNOCHEMOTHERAPY WITH CD20-ANTIBODY RITUXIMAB, HIGH-DOSE CYTOSINE-ARABINOSIDE AND MITOXANTRONE IN PATIENTS WITH LOW-GRADE LYMPHOMA

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Introduction: Myeloblastic therapy including total body irradiation and high-dose cyclophosphamide with peripheral blood stem cell (PBSC) transplantation is a treatment modality for patients (pts) with advanced-stage follicular lymphomas and can result in 78% relapse-free survival after 6 years when performed in first remission. Contamination of PBSC products by tumor cells can contribute to relapse of the disease after transplantation, while the selection of hematopoietic CD34+ stem cells may reduce the risk of reinfection of tumor cells. The reduction of the tumor burden in vivo before PBSC collection might as well contribute to an increase in the probability of a tumor-free transplant.

Methods: In an attempt to intensify the tumor reduction, we included the humanized chimeric anti-CD20 antibody Rituximab on day -1 into our mobilization regimen consisting of high-dose cytosine-arabinoside (2 g/m² q 12 hours, days 1 and 2) and mitoxantrone (10 mg/m², days 2 and 3) (HAM). So far, 10 pts were enrolled into our study, 8 pts with follicular and 2 pts with mantle cell lymphoma. All pts had stage IV disease.

Results: The Rituximab antibody was very well tolerated without serious side effects. Leukaphereses were performed during the G-CSF-supported leukocyte recovery after HAM, and in all patients, CD34+ cells were enriched by an immunomagnetic method. In all but one pt, a sufficient number of CD34+ cells could be recovered after enrichment for the support of high-dose therapy, considering 2.5 x 10^6 CD34+ cells/kg body weight as threshold number (median 4.9, range 1.5 - 13.6 x 10^6/kg). The content of B cells in the leukapheresis products was assessed by CD19 staining demonstrating a low median proportion of 0.08% range 0.00 - 2.02%. This translates into a median absolute number of 8.3 x 10^4 CD19+ cells/kg (range 0-131). The immunoselection further reduced the amount of B-cells to a median of 0.2 x 10^6/kg. Bone marrow or peripheral blood specimens of 5/6 pts with follicular lymphoma were t(11;18)-PCR positive before mobilization therapy, while only one patient had a PCR-negative leukapheresis.

Conclusion: The addition of the humanized CD20 antibody to the HAM-chemotherapy is safe and well tolerated, and allows the collection of PBSC products with a high purity and collection efficiency in pts with low-grade lymphoma.

SHORT COURSES OF CHEMOTHERAPY FOLLOWED BY AUTOLOGOUS HAEMATOPOIETIC STEM CELL TRANSPANTATION IS AS EFFECTIVE AS STANDARD PROLONGED THERAPY IN ADVANCED HIGH-GRADO NON-HODGKIN'S LYMPHOMA

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Aim: To compare the efficacy of double-CHOP-Dexa-BEAM followed by transplantation of haemopoietic cells and conventional prolonged regimes (Hoelzer 1989, Kantarjian 1992)

Patients and Methods: 30 patients with high grade NHL (III-IV) were included. Immunophenotyping was performed on histological lymph node sections. First group (16 patients) were treated by two cycles of CHOP and Dexa-BEAM. In some of them Dexamethasone pulses were used to debulking the disease before Dexa-BEAM. Dexam-BEAM was followed hematopoietic cell harvesting (6 bone marrow, 5 peripheral stem cell apheresis, 5 both) and transplantation with CBV or BEAM conditioning regimen. Second group (14 patients) were treated according to conventional prolonged regimes. According to gender and age two groups were comparable

Results: CR+PR rate was 81% versus 50% (p=0.08) in two groups. OAS was 84% versus 50% (p=0.065). DFS was 84% versus 49% (p=0.24). OAS and DFS are presented at 4.5 year.

Conclusion: Double-CHOP-Dexa-BEAM followed by haemopoietic cell transplantation is comparable to conventional prolonged therapy. CR+PR and OAS tends to be better in the first group.

Autologous stem cell transplantation in follicular lymphoma with high tumor burden: a single center experience.

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From 1994 to 1997, 38 patients with histologically proven high tumor mass follicular lymphoma (FL) received an autologous stem cell transplantation (ASCT). All the patients were FL with high tumor burden defined by at least one of the following criteria: presence of B symptoms, nodal or extranodal site > 7 cm, complications as compression or serious effusion, massive splenomegaly or increased LDH.

Our series comprized 24 men and 14 women. Median age was 39 years (range: 22-60). Histology was follicular predominantly small cell in 8 cases, follicular mixed in 28 cases and follicular predominantly large cell in 2 cases.

At ASCT, 25 patients were in CR1 or PR1 and 13 in CR2 or PR2. Sixteen patients received unpurged graft (marrow 8, PBPC 8). Twenty two patients had purified graft (marrow 18, PBPC 4), 7 with adjusted dose of cyclophosphamide derivatives, 7 with an anti-B cell monoclonal antibodies plus complement, 4 with anti B-immunomagnetic system (Baxter), and 4 had positive selection of CD34+ cells (Baxter). All patients were conditioned with TBI followed by cytoxan (29 patients) or BEAM (9 patients).

Median follow-up is 69 months (range: 15-25 months). After ASCT, CR was achieved in 35 patients. Two toxic deaths were observed. Actuarial survival at 5 years was 81% overall (OS), 72% disease-free (DFS) and 61% event-free (EFS). The effect of purging was assessed. The 5 years DFS is 72% and 71% (p=0.48) for unpurged and purified patients respectively. The outcome of patients grafted in CR1 or PR1 is not different compared to more advanced patients (5 years DFS = 74% versus 67%, p=0.68). At the present time, waiting for failure of first line therapy to perform ASCT does not seem to modify the prognosis as compared to ASCT in first line.

Successful peripheral blood progenitor cell mobilization with etoposide (VP-16) in patients with relapsed or resistant lymphoma who failed cyclophosphamide mobilization

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High-dose chemotherapy (HDCT) followed by autologous blood stem cell transplantation is considered the treatment of choice for patients with relapsed or resistant aggressive non-Hodgkin's lymphoma (NHL) or Hodgkin’s disease (HD). However, several authors report a failure to standard mobilization regimens in 25% to 56% of these patients making the completion of HDCT impossible and, as a result, negatively influencing long-term outcome. Thus, effective new regimens for patients failing initial mobilization are needed. We report the results of etoposide as a mobilizing agent in 16 patients with primary resistant or relapsed malignant lymphoma who had failed prior mobilization of peripheral blood stem cells (PBSC) with cyclophosphamide (4 g/m²) followed by G-CSF. The use of etoposide 500 mg/m² (1-4) + G-CSF resulted in the successful collection of adequate numbers of PBSC with a median harvest of 3.6 x 10^7/kg (range 2.2-12.6) CD34+ cells in all 16 patients. In 7/16 (44%) patients, the target yield of at least 2.0 x 10^6 CD34+ cells was harvested by a single apheresis and the maximum number of separations for all patients was two. No excessive toxicities appeared, allowing all patients to proceed to myeloablative chemotherapy. In addition, median peak values of circulating CD34+ cells were significantly higher after etoposide as compared to cyclophosphamide (49.2±0.4 vs. 4.7±0.1; p=0.0004). These results indicate that etoposide + G-CSF is a highly effective mobilization regimen in patients who have failed cyclophosphamide mobilization.

8. High Dose Therapy
TANDEM HIGH-DOSE THERAPY (HDT) WITH STEM CELL SUPPORT FOR ADULTS WITH POOR PROGNOSIS LYMPHOMAS: RESULTS OF A PILOT STUDY OF THE GOELAMS.
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With conventional therapy patient (pts) with intermediate/high grade NHL having high-risk features of the international prognostic index at DG (HR) or with refractory disease or early relapse (5 y from dg) and pts with disseminated transformation of low grade NHL (TLG) have a poor prognosis. For pts from 5 to 60 y o we designed a pilot program including a tandem HDT with autologous PBSCT support. De novo HR pts and TLG pts received 2 courses (C1 and C2) consisting of Cytoxan 1.2g/m² iv d1, Epirubicin 100mg/m² iv d1, Cytosar-U 3g/m² iv d1, Prednisone 60mg/m² po d1-5 and C2 started at day 15. Each course was supported with G-CSF (5mg/kg/d sc) and PESC were harvested on d12, 13, 14 of C1 and d12, 13 and d14 of C2. Pts with refractory disease or early relapse received 2 courses of salvage therapy (ESHAP) and PBSCT were harvested after the 1st course and 2nd course.

First HDT (C3) consisted of Mitoxantron 45mg/m² iv d1 and Cytarabine 1g/m² iv (3h infusion) d1 to d4 followed by the injection of half of the harvested PBSCT. Second HDT (C4) consisted of 1.2 g Cyfrationed TBI followed by BCNU 300mg/m² iv d1, Etoposide 200mg/m² iv d1 and Cytoxan 150mg/m² iv d1-4 (CBV) or Cytoxan 60mg/kg iv d1-2. The remaining PBSCT were used as autologous support. Forty two pts have been included, age 17 to 60 (med: 50 y). 34 pts were de novo HR, 6 pts were refractory or early relapse and 3 pts had TLG. Thirty nine pts had stage IV, 23 had BM involvement, the median n° of extra nodal sites was 2. Overall this program was completed in 37/42 pts (90%). The 1st and 2nd courses were well tolerated and well (eval 15 pts), 11 pts either progressed or relapsed a median of 5 months (1-13m) after start of C1 and 6 toxic death occurred. Of the 37 pts who completed the program, the toxic death rate after TBI +CBV was 5 out of 19 pts (26%), no toxic death were seen in 18 pts (94%) who received TBI +Cytoxan. Seven pts relapsed (5 after TBI +Cytoxan and 2 after TBI +CBV). This program is feasible and effective in adults pts with poor prognosis intermediate or high grade NHL including those (>50%) with BM involvement.
IPI SCORE HAS A PROGNOSTIC VALUE IN NON-HODGKIN'S LYMPHOMA PATIENTS TREATED UPFRONT WITH HIGH-DOSE SEQUENTIAL CHEMOTHERAPY AND AUTOGRRAFT


Introduction: IPI (International Prognostic Index) is the most widely accepted scoring system to predict outcome following conventional chemotherapy in both low and intermediate/high grade non-Hodgkin's lymphoma (NHL). The present study was aimed to verify whether IPI has predictive value in high-dose sequential chemotherapy (HDS) programs with peripheral blood progenitor cell (PBPC) autograft as well.

Methods: The study was carried out in 88 pts. (median age: 48 yrs., range 18 - 61) with high-risk NHL (40 low-grade; 48 intermediate/high grade). The age-adjusted IPI system identified: 1 pt. with score 0, 28 with score 1, 32 with score 2 and 27 with score 3. All pts. received upfront a program including: i. sequential hd-drug administration (cyclophosphamide 7 g/m², methotrexate 8 g/m², etoposide 2 g/m²); ii. submyeloablative treatment with PBPC autograft; iii. RT on bulky sites. Overall (OS) and Event Free (EFS) survival were evaluated in IPI subgroups; in multivariate analysis IPI was matched against other parameters, including histology, sex, age < or > 45 y, BM involvement.

Results: At a median follow-up of 2.8 years, the estimated 5-year OS and EFS for the entire group were 68% and 49%, respectively. When IPI subgroups were analyzed, the estimated 5-year OS was 93%, 75% and 52% for patients with IPI score 1, 2 and 3, respectively (p=0.0014). Similar differences were observed for EFS. In multivariate analysis, IPI score ≥ 2 had a significant adverse prognostic value for both OS (RR 2.9, p=0.0009) and EFS (RR 2.3, p=0.003).

Conclusions: IPI is suitable to predict response and life expectancy also in NHL pts. managed upfront with hd-chemotherapy and autograft.

TOXICITY AND FEASIBILITY OF AN INTENSIFIED SEQUENTIAL CHEMOTHERAPY REGIMEN IN ELDERLY NON-HODGKIN'S LYMPHOMA PATIENTS


Introduction: In the last years, promising results have been reported on the use of high-dose (hd) sequential chemotherapy as an alternative to conventional polichemotherapy in the management of adult NHL patients.

We have evaluated the applicability of this strategy in elderly patients.

Methods: The study was addressed to evaluate an intermediate-dose sequential chemotherapy (IDSC) regimen, including the administration every 2-weeks of: etoposide 120 mg/m² + vincristine 2 mg; cyclophosphamide 4 g/m²; etoposide 1.5 g/m²; the sequence is repeated twice, for a 6 total courses. RT is then given on bulky sites. G-CSF is administered following each course. So far, 47 pts. received IDSC. Their main clinical features were: median age=68 yrs. (range 60-76); M/F ratio=22/25; histologic subtype: Burkitt's 1; DLCL=31; mantle-cell=5; low grade=12; BM involvement=19; high LDH=23; Stage III-IV=38; Performance Status 22-26; recurrent disease=6.

Results: Four pts. did not complete the program for disease progression; the remaining 43 pts. were able to complete the whole program without severe complications. There were no toxic deaths. Median duration of the regimen was 104 days (range 62-224). Sixteen pts. (34%) had fever (median duration: 7 days); 5 pts. had pneumonia and 1 acute pericarditis, resolved after i.v. antibiotics. PRBC and/or platelet transfusion support was required in 37 pts. Presently, 35 pts. are alive, at a follow up ranging between 6 mos. and 4 years since enrollment in the IDSC program.

Conclusions: A chemotherapy strategy based on intermediate-dose single-agent sequence is a feasible option in elderly NHL pts., with an overall toxicity similar to that recorded with conventional regimens.

SHORT INTENSIVE TREATMENT WITH HIGH DOSE CHEMOTHERAPY IN PATIENTS WITH AGGRESSIVE NON-HODGKIN'S LYMPHOMA (NHL) WITH 2 OR 3 POOR PROGNOSTIC FACTORS

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Introduction: Patients with NHL and 2 or 3 factors of the International Prognostic Index (IPI) have a poor prognosis. We performed a prospective trial of early intensification in such patients.

Methods: Thirty patients (pts) were included. The median age was 38 yrs. (range 15-59). Fifteen pts had 2 IPI factors and 15 had 3 factors. Nine pts had bone marrow involvement. The patients received 2 to 3 courses of the ACE protocol (Adriamycin D1; cyclophosphamide D1-2; etoposide D1-3), with G-CSF support. Depending on the quality of remission after induction, patients then received one or two intensification courses with peripheral stem cell support.

Results: Twenty four patients received intensification, including 9 pts who received a second high dose treatment. Three patients relapsed after intensification. Six patients did not proceed to intensification: one because of lethal lysis syndrome during the first course of ACE, three because of progressive disease, one because stem cells could not be collected and one because of altered performance status. With a median follow-up after first chemotherapy of 16 months, the overall survival was 77% with a tendency towards a plateau. All deaths and relapses have occurred within 7 months of the beginning of chemotherapy.

Conclusions: Early therapeutic intensification after intensive induction chemotherapy is feasible in patients with poor prognosis aggressive NHL and shows promising survival rates.

COST-EFFECTIVENESS COMPARISON OF AUTOGLOUS THERAPY VS RELAPSE


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Introduction: Intensive chemotherapy and autologous bone marrow transplant (ABMT) have shown promising results for relapsed diffuse large cell lymphoma (DLCL) and in first remission for high-intermediate stage disease (R/ID). For low-intermediate stage disease (LID) results for ABMT in first remission are less conclusive. This study estimates the cost-effectiveness of ABMT in first remission for LID and R/ID DLCL, in comparison to standard anthracycline-based therapy (with ABMT for relapsed patients).

Methods: Decision analytic modeling was used to determine the cost-effectiveness of each treatment strategy, accounting for relapse, salvage treatment (letherepsis), disease progression (DHPA) and survival for the first five years post treatment. Clinical estimates for each decision node were obtained from the scientific literature, corroborated from clinical experience at the Centre Léon Bérard. Cost estimates for each treatment (total costs (1996 SUS) through 100 days post therapy) were obtained from the Northwestern University/ Autologous Blood and Marrow Transplant Registry Economic Data Base. Sensitivity analysis were conducted for each case in order to estimate the range of total costs.

Results: The cost per 5-year survivor for H/HD was $104,340 for chemotherapy and $180,659 for ABMT; the cost per 5-year survivor for LID was $43,671 and $119,334, respectively. The marginal cost-effectiveness of ABMT compared to chemotherapy was $394,223/ additional survivor for H/HD and $722,499/additional survivor for LID. Sensitivity analyses show that the cost per 5-year survivor for ABMT remain higher than chemotherapy over the published range of survival rates and stable estimates of costs. However, when the best case scenario is utilized for ABMT for H/HD, the marginal cost effectiveness is $120,125/ additional 5-year survivor. If the median survival of these patients is equal to 3 years, the cost per life year gained would be $40,042, within conventionally acceptable limits.

Conclusion: ABMT in first remission for DLCL is potentially cost-effective for H/HD patients. As the cost of transplant decreases, through the use of blood stem cells or outpatient protocols, or survival improves this may become a more attractive strategy for H/ID patients. Better evaluations of long-term survival of ABMT patients are needed to provide more accurate estimates of cost-effectiveness.
Dexa-BEAM (DB) Program for Patients with Malignant Lymphomas

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The DB program was suggested in 1989 by Pfreundschuh et al. for the treatment of refractory and relaps of Hodgkin's disease. Since 1995, 44 patients: 39 with Hodgkin's disease and 5 with high grade lymphoma had received this program in one clinic.

Results: 19 patients (43%) achieved complete remission: 6 of them were resistant to MOPP-ABVD, Stanford V, COPP-ABVD, CHOEP, MACOP-B therapy; 6 - with relapses which occurred after these courses and unprogrammed polychemotherapy courses; 5 - with progressive disease on the first line therapy, including mentioned courses.

These patients received from 1 to 4 courses. The follow-up from 2 to 28 months. Refractory or progressive disease were observed in 24 patients (57%). 8 patients had died of sepsis without remission.

All chemotheraphy courses were complicated with agranulocytosis and thrombocytopenia, and most patients had the following complications: sepsis, hematagic syndrome.

Conclusion: DB is an available therapy, without peripheral blood and bone marrow stem-cell support, for patients with malignant lymphomas, after relapse or refractory to the front-line therapy. The program gives about 40% of complete remission.

The preliminary results showed that group of patients with progressive disease after the front-line therapy is the least favourable.

3. This program should be carried out in a well-equipped hospital and with a qualified staff.

High-dose sequential chemotherapy (HDC) and peripheral blood stem cell (PBSC) transplantation for patients with relapsed or refractory aggressive non-Hodgkin's lymphoma (NHL). Unexpected TTP toxicity and a low probability of cure.


Purpose: to assess the feasibility and efficacy of five high-dose sequential chemotherapy courses that include three intensified cycles in relapsed or refractory NHL patients and methods: Ten patients (9 NHL) with refractory (n=8) or relapsed (n=2) NHL were included. The five phases of HDC consisted of Step I (cyclophosphamide, etoposide, lenogranium [G-CSF], and PBSC harvest), Step II (cytarabine, cisplatin, etoposide and G-CSF), Step III and IV (cyclophosphamide, etoposide, cytarabine and PBSC infusion, and lenogranium and Step V (carmustine, etoposide, cytarabine and melphalan, PBSC infusion and G-CSF).

Anticancer agents

- Total dose planned (16 weeks)
  - Cyclophosphamide: 11,000 mg/m²
  - Etoposide: 140 mg/m²
  - Cytarabine: 11,000 mg/m²
  - Cisplatin: 3,500 mg/m²
  - Carmustine: 100 mg/m²
- Total dose received
  - Cyclophosphamide: 10,000 mg/m²
  - Etoposide: 100 mg/m²
  - Cytarabine: 1000 mg/m²
  - Cisplatin: 1000 mg/m²

- drug toxicity
  - Grade 3 and 4 toxicity: 0%

- Hematologic toxicity: 100% (neutrophils)

- Non-hematologic toxicity: 50% (neurological, hepatic, gastrointestinal)

- Results: Six patients (60%) did not complete HDC, one due to failure of peripheral blood stem cell harvest, one due to thrombotic thrombocytopenic purpura (TTP) after Phase IV and four due to NHL progression. 4 pts completed the protocol and received the planned doses in 16 weeks. One died of toxicity (interstitial pneumonitis 6 weeks after the end of therapy). Mucositis and hematologic toxicities were not limiting. Unexpected major toxicity was thrombotic thrombocytopenic purpura which occurred in three patients after Step III (w=1), IV (w=1) and V (w=1) and led to severe chronic renal failure in one.

- Three pts are in persistent CR: 1 of the eight refractory patients (10 months) and the 2 pts with relapsed NHL (10+ and 14 months+).

Conclusion: On this short series, despite very intensive cyclophosphamide, VP16, cytarabine based salvage regimen, our results were very disappointing in refractory pts. An unusual TTP rate was observed during therapy.

Primary diffuse large B-cell lymphoma of the mediastinum (PMCL): High rate of sustained complete remission (CR) with peripheral blood stem cell transplantation (PBSCT) as an early intensification treatment.


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Introduction: PMCL is an aggressive, locally invasive, B cell lymphoid tumor now recognized as a distinct clinicopathologic entity in the REAL classification. Clinical outcome after conventional treatment is characterized by an high rate of relapse but recent reports suggest that high-dose chemotherapy with autologous stem cell transplantation can induce durable remission.

Methods: We performed a retrospective analysis of 18 patients with locally advanced PMCL, referred to our institution from 1983 to 1998 and included in our autologous transplantation program. The median age was 34.9 years (range 21-62); 14 were females and 4 were males. A first series of 8 patients was treated with MACOP B (8 weeks), HAM and BEAM conditioning regimen; the more recent group of 10 patients was treated with the sequential APO, HDS, MTOLO-PAM protocol. Nine patients received consolidation radiotherapy after PBSCT.

Results: Four patients were in CR at the day of transplant. The patients did not complete the transplantation program three for intercurrent diseases (tuberculosis, stroke and psychiatric disease); one patient died of irreversible cardiac failure soon after high dose Cyclophosphamide. Of the 14 patients actually transplanted, 2 died of tumor progression shortly after PBSCT. A double PBSCT was performed in one of them without result. The remaining 12 patients achieved CR, none relapsed with a median followup of 22.5 mo. (range 3-39). In an intention-to-treat analysis 14/16 patients (77%) are alive and in CR including 2 not transplanted.

Conclusion: Our data suggest that an early intensification treatment with PBSCT may increase the CR rate and reduce the risk of relapse in PMCL.
THREE STEP HIGH-DOSE CHEMOTHERAPY IN INTERMEDIATE RISK NON-HODGKIN LYMPHOMA.
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Patients and methods. Thirty patients (pts) with intermediate-high risk (13), low-intermediate risk (17) according to international prognostic index non-Hodgkin’s lymphomas (NHL) received HDT, 22 of them either as first line treatment (10) or as consolidation after conventional dose chemotherapy (12), and 8 at relapse (4) or with refractory disease (4). Histologic subtypes were diffuse large cell (27) and anaplastic large cell (3). HDT included three phases: 1) cyclophosphamide 6-7 g/m² day 1 with GM-CSF support, 5-8 µg/kg/day, days 2-14 and PBPCs collection, 2-4 leukaphereses; 2) mitoxantrone (NGV) 60-120 mg/m² day 4 ± melphalan (L-PAM) 160-200 mg/m² day 1 and PBPCs rescue; 3) etoposide (ETO) 500 mg/m²/day + carboplatin (CARBO) 500 mg/m²/day days 3-7, -2, -1 and PBPCs rescue. Results. After PBPCs reinfusion haematologic recovery was fast and complete with a short duration of neutropenia and thrombocytopenia. The main nonhaematologic toxicities were mucositis and diarrhoea. In the first line/consolidation group, after a median follow-up of 3 years, 18 of the 22 pts are alive and disease-free (82%), 3 relapsed (at 7, 10 and 14 months) and 2 died at 14 and 20 months, 1 is alive at 34 months; 1 pt did not respond to HDT and died of progressive disease. The projected survival at 5 years is 84%. Only two of the pts treated at relapse or with refractory disease (25%) are disease free (at 15 and 34 months); both had relapsed after first line treatment and were responsive to salvage therapy. Conclusions. When used in the setting of first line or consolidation treatment the HDT herein described was a safe and effective regimen for intermediate risk NHL and might represent a substantial improvement in terms of response to conventional chemotherapy. In our experience HDT was useful in pts with relapsed and responsive disease but had not efficacy in primary refractory patients.

8. High Dose Therapy
F-MACHOP: RT + ASCT AS FIRST LINE THERAPY FOR AGGRESSIVE INTERMEDIATE-HIGH GRADE NHL


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We investigated the outcome of a group of patients with intermediate-high grade NHL, who were considered for a first-line therapeutic program based on 6-F-MACHOP courses (prednisone + vincristine + cyclophosphamide + Adriamycin + 5-fluorouracil + methotrexate) + involved field radiotherapy on localized disease + high-dose therapy (BACV conditioning regimen) and autologous stem cells transplantation (ASCT). To enter into the study, patients had to be ≤ 60 yrs and have almost one of these adverse prognostic factors: stage III-IV, B symptoms, bulky disease. Seventy-three patients were enrolled between July 1991 and August 1997. Results were evaluated with an intention to treat analysis. Median age was 42 years (range 16-77). According to the age adjusted International Prognostic Index (IPI), 12 (16%) patients had score 0, 34 (46%) score 1, 26 (32%) score 2 and 11 (15%) score 3. Response rate after F-MACHOP (CR + PR) was 91%. Twenty out 73 (27%) patients did not performed ASCT, 14 due to resistance (10 patients) or toxicity (4 patients). We attempted F-MACHOP and the remaining 6 for other causes (secondary tumor 1, harvest failure 2, patient refusal 3). Thirteen of the 27 patients (48%) with IPI score ≥ 3 did not perform ASCT, the majority of them (7) due to primary resistance to induction therapy. After a median follow-up of 37 months (range 1-88) 54 patients (74%) are alive and disease free. A worse outcome was observed for patients with unfavorable IPI scores 3-5 (66% vs 0-1, p = 0.01) and for patients who did not perform ASCT (89% vs 35%). Furthermore, for patients with IPI score ≥ 2, 3, a strict association between outcome and ASCT was evident (ASCT vs no ASCT, 79% vs 15%). Transplant related mortality was registered in 2 cases. Delayed toxic events after ASCT were reported in 23 cases (second tumor 1, herpes zoster 3, peripheral neuropathy 2, autoimmune syndrome 2, femoral head aseptic necrosis 1, myocardipathy 1, ITP 2, ipogamaglobulinemia 11). Our results suggest the role of ASCT as first line treatment, and furthermore emphasize the necessity of an intensification of induction therapy for the category of patients with IPI score ≥ 3.


In order to improve the complete remission (CR) rate in patients with follicular lymphoma (FL), we designed the following intensive combined regimen: (1) 2 monthly cycles of C2H2OP; (2) high dose Melphalan (140 mg/m²) supported by peripheral blood stem cells (PBSC) collected after C2H2OP; (3) Cyclophosphamide (120 mg/kg) and TBI (12 Gy, 3 fractions) supported by bone marrow and PBSC. (4) INF alpha started within the 90 days following the second grafting. Residual disease was evaluated by molecular biology: the bcl2/hlg16 junctional region was sequenced in order to synthesize a clonospecific probe for each patient. From 02/94 to 02/98, 39 patients (pts) have been included (stage III-IV; 1V=31), 28 were previously untreated and 11 in first relapse. Median age was 46 years (25-65). The feasibility was satisfactory: 36 pts received the first intensification and 35 pts the second (2 pts are still waiting, 2 were excluded for hematopoietic toxicity). The overall toxicity was acceptable. No toxic death occurred. The median durations of neutropenia (<0.5x10⁹/l) and of thrombopenia (<20x10⁹/l) were 7 days (4-17) and 1 days (0-28) for the first intensification and 12 days (9-35) and 7 days (0-60) for the second. The median number of ABC and platelet transfusions was 0 (0-7) and 1 (0-6) for the first intensification and 2 (0-22) and 4 (0-21) for the second. Median duration of hospitalisation was 15 days (9-23) and 24 days (12-65) for first and second intensification, respectively. The complete response rate (CR) was satisfactory: 33/34 (97%) clinically evaluable pts were in CR and 7/11 pts (54%) evaluable for molecular residual disease had a complete response. With a median follow-up of 35 months (3-52), 8/37 clinical relapses occurred and, only 3/14 pts remained in molecular CR. The 4 year post-inclusion probability of EFS was 70% (95% CI). Finally, CR rate and EFS were satisfactory. However, despite this intensive regimen, a molecular residual disease was still detectable in most patients.

AUTOLOGOUS STEM CELL TRANSPLANTATION IN CARRIERS OF HEPATITIS B AND HEPATITIS C VIRUS

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Hepatitis B virus (HBV) reactivation may result in hepatitis, hepatic failure and death. This has been documented following both chemotherapy (CHT) withdrawal and high-dose therapy; in several cases the detection of HBVAg prevents from performing the transplant procedure. Less is known about hepatitis C virus (HCV) carriers undergoing standard and high-dose CHT. In this study we report on the outcome of 11 patients (pts) (6 carriers of HCV-RAV and 5 of HClAg) who were autotransplanted at our Institution between March '92 and June '98. M/F ratio was 7/4, median age 41 years (25-56). Nine pts (4 HBsAg and 5 HCV-RAV) were affected by non-Hodgkin’s lymphoma (NHL), 1 (HCV) by chronic myelogenous leukemia (CML) and 1 (HClAg) by breast cancer (BC). The patient with CML was treated with IFN and conditioned with Busulfan/Melphalan. The patient with BC was treated with 6 TEC and then conditioned with Thiopeta/Cyclophosphamide. All the NHL pts were treated with F-MACHOP and conditioned with BAVC. In the immediate post-transplant period in only 1 patient (HBsAg carrier and affected by BC) a hepatitis was documented (at about 1 month from ASCT) with an elevation of transaminase levels (x20-40 n.1) not associated with the detection of HBV DNA. According to the definition of Lau et al. this pattern can be defined as hepatitis (probably drug-induced) but not as hepatitis B virus reactivation. No other complication, no toxic deaths were observed. During post-transplant follow-up median 29 months, range 7-81) no hepatic abnormalities were observed. Overall survival of the whole population is 54 months (18-124). Currently 10/11 pts are alive in complete remission, while 1 patients affected by follicular centre lymphoma is alive with disease 50 months from ASCT. This study shows that ASCT can be performed safely in HBsAg and HCV-RAV carriers.

HIGH DOSE IDARUBICIN AND MELPHALAN AFTER SEQUENTIAL HIGH DOSE CHEMOTHERAPY (S-HDC) FOR LYMPHOMAS: PRELIMINARY RESULTS OF A PHASE III STUDY WITH PHARMACOKINETICALLY ASSAYED


Introduction: S-HDC with peripheral autologous stem cell support is often used in poor risk non-Hodgkin’s lymphomas (NHL) and Hodgkin disease (HD). Idarubicin (IDA) demonstrated significant activity in NHL but no data is available on its use in continuous infusion. In order to verify its clinical activity and the bioavailability of its active metabolite idarubicinol (IDOL), 27 patients (pts) with NHL and HD underwent to S-HDC for relapsed, resistant or poor risk patients.

Protocol characteristics. Median age: 39 yrs; History: 12 pts were affected by large B cell; 4 by follicular, 1 by mantle, 3 by peripheral T cell and 1 by NK NHL; the 6 pts with HD were affected by nodular sclerosis. Methods: IDA was administered at escalating dosages from 12 to 17 mg/m² d1-3 i.v. as continuous infusion, followed by melphalan 180 mg/m² d5. Day 7 was chosen for PBSC reinfusion. Pharmacokinetic assay was performed in 14 pts; blood samples were obtained during IDA administration and at day 3-9. Toxicity. The median number of days to reach 1 x 10⁹ WBC/ml was 14 (range: 11-20) and to reach 10 x 10³ PLT/ml was 12 (range: 11-40). The dose limiting toxicity was G3 mucositis, which occurred in 35% of pts for a median of 4 days and in all pts treated with a dosage higher than 15 mg/m². No engraftment failure was observed, even if high dose level of IDOL (11.7 nM, range 3.3-17.4) were detected at the time of reinfusion. Results. 16 pts achieved complete remission (CR), 6 pts partial remission and 5 pts for response is not evaluable. Relapse occurred in 9 pts. 6 pts died of disease and 10 of sepsis. With a median follow-up of 14 months 13 pts are alive and disease free. Conclusion. In our experience IDA administered in combination with melphalan has a substantial clinical activity, at least superimposable to other conditioning regimens. We suggest 15 mg/m² as an optimal dosage. Reinfusion on day 7 is safe because IDOL concentration in vitro is not predictive of citotoxicity in vivo.
RITUXAN BEFORE AND AFTER HIGH DOSE CHEMOTHERAPY (HDC) WITH STEM CELL SUPPORT FOR RELAPSED AGGRESSIVE LYMPHOMA

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BACKGROUND: Relapse is the leading cause of treatment failure following HDC. The anti-CD20 monoclonal antibody, Rrituxan, is approved for the treatment of relapsed indolent lymphoma and is effective in clearing blood and marrow of lymphoma cells. This study uses Rituxan as an in vivo purging agent before and after peripheral blood stem cell harvest and transplantation. Patients (pts) must have a working formulation intermediate grade CD20-positive lymphoma which has relapsed or is refractory to initial chemotherapy, but is sensitive to a salvage regimen. The first dose of Rituxan was 375 mg/m² followed in one week by 500 mg/m². After a two week interval, peripheral blood stem cells were collected after priming with growth factors. HDC consisted of BCNU/Etoposide/Cytosox or TBI/Etoposide/Cytosox. Following hematologic recovery and before day +42, patients received two weekly infusions of Rituxan at 500 mg/m².

RESULTS: Six pts have been enrolled, five pts have completed all phases of the protocol. One pt relapsed prior to cell collections and did not proceed to HDC. The median age is 47 yr (39-60). All pts had diffuse large histology. Three relapsed after a CR and two progressed on initial therapy. All pts were sensitive to salvage therapy. All pts tolerated the Rituxan without any side effects. Engraftment was prompt with a median time to ANC > 500 and platelets > 20,000 of 10 (9-15) and 13 (12-15) days, respectively. The median number of PBPC and platelet transfusions was 4(6) and 3(5), respectively. All five pts are in remission 37- to 55+ days post HDC.

CONCLUSIONS: Rituxan before and after a BMT for B-cell lymphoma is well tolerated and deserves further evaluation as a means of improving disease free and overall survival.

TREATMENT OF PATIENTS WITH RELAPSED OR REFRACTORY INDOLENT LYMPHOMA USING DEXAMETHASONE, BCNU, ETOPOSIDE, ARA-C, AND MELOPHAN (DEXA-BEAM) FOLLOWED BY HIGH DOSE CHEMOTHERAPY AND STEM CELL RESCUE - A HIGHLY EFFECTIVE TREATMENT PROGRAM

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Introduction: To determine the efficacy of maximal cytoreductive therapy with up to four cycles of Dexe-BEAM (dexamethasone, BCNU, etoposide, Ara-C, and melphalan) followed by high-dose chemotherapy (HDCT) and autologous hematopoietic stem cell support (ASCT) for patients with advanced relapsed or refractory indolent lymphoma.

Methods: Thirty-three patients with primary refractory or relapsed indolent lymphoma were treated with the Dexe-BEAM regimen. Fourteen patients had primary refractory disease, seven patients partial remission, and 12 patients complete remission after HDC. All patients were eligible for ASCT. The conditioning regimen used was BEAM (BCNU, etoposide, Ara-C, and melphalan).

Results: Twenty-five patients responded to Dexe-BEAM resulting in a response rate of 76%. 93% of patients with primary refractory disease, 71% of patients with partial remission, and 78% with relapsed lymphoma responded. Maximum response was observed after 3.2 (range 2-5) courses. One patient with progressive disease died due to septic shock during neutropenia. Eighteen patients received partial or complete remission after Dexe-BEAM received HDC. Hematopoietic stem cells (HSC) were collected after two cycles of Dexe-BEAM. The median number of CD34+ HSC infused was 3.0 x 10^6/kg (range 1.5-8.2 x 10^6/kg). All patients receiving HDCT achieved complete remission. Overall survival and freedom from treatment failure for all patients are estimated to be 54% and 36% at three years, respectively. With a median follow-up of 33 months (range 7-33 months), 14 patients receiving HDCT are in continuous complete remission. There was no transplantation-related death.

Conclusions: The Dexe-BEAM regimen is effective in overcoming drug resistance in patients with indolent lymphoma who failed to respond to conventional chemotherapy or who relapsed. The CR rate of 100% of those patients receiving HDCT and ASCT after maximal cytoreductive treatment with Dexe-BEAM suggests the use of HDCT at the time of maximal response.

AUTOLOGOUS PERIPHERAL STEM CELLS TRANSPLANTATION IN HEAVILY PRETREATED PATIENTS WITH NON-HODGKIN’S LYMPHOMA.

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Purpose: To assess the feasibility and the efficacy of HSCT followed by autologous peripheral blood stem cell (PBSC) transplantation in heavily pretreated patients with Non-Hodgkin’s Lymphoma (NHL).

Patients and methods: Sixteen patients, 9 male and 7 female, median age 39 years, range 26-60 years with relapsed (9 patients) or refractory (7 patients) NHL were referred between 1993 and 1998 for PBSC collection before high dose (HD) chemotherapy. Twelve patients had diffuse large cell lymphoma, two had diffuse mixed cell type and two had diffuse small cleaved cell type. The patients had stage IV disease (n=8), stage III (n=6) and stage II (n=2).

The median number of previous courses of chemotherapy was 12 (range 4 to 24). The mobilization procedure was performed in 2 patients with GC-SF alone, 5 patients received MAD chemotherapy plus G-CSF and 9 received high dose Cyclophosphamide with G-CSF. Conditioning regimen consisted of BEAM (n=6), Bu-Cy (n=2), Mitox-L-PAM (n=1) and Thi-Tepa-L-PAM.

Results: The median number of sbpheresis procedures was 2.2 (range 1 to 5) resulting in a median of 6.6 x 10^6 CD 34+ cells/kg. Hemopoietic reconstitution, blood and platelets transfusions support, infectious complications and overall hospitalization were not different from those recorded in patients with a primary indications for autologous PBSC transplantation.

All patients but one reached the target of 2.0 x 10^6 CD 34+ cells/kg; 2 died for progression after mobilization of PBSC, 2 did not performed PBSC transplant and 2 are too early for evaluation. Of the remaining 9 patients, 3 died for progression of lymphoma at 5, 23 and 37 months, 6 achieved a complete response and all are alive at 1, 2, 4, 7, 17 and 60 months.

Conclusions: Adequate PBSC mobilization can be obtained in heavily pretreated lymphoma patients and HD chemotherapy with autologous PBSC transplantation can be employed as salvage treatment for this patients. However, we need a much longer follow-up in the efficacy validation of this treatment.

COMPARISON OF CARDIAC TOXICITY OF STANDARD-DOSE VERSUS DOSE INTENSIFIED EPIRubicIN PLUS CYCLOPHosphAMIDE IN PATIENTS WITH NON-HODGKIN’S LYMPHOMA (NHL).

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Introduction: Cardiac toxicity remains a major concern following ABVD, with a cumulative incidence of death from acute myocardial infarction (AMI) of 5% and that of congestive heart failure (CHF) at 10% at 10 years. The ANZLG initiated a randomized phase III clinical trial in patients with intermediate-grade NHL comparing standard-dose CEP (CEPAB) and dose-intensified CEP (COPAB) to assess the feasibility and efficacy of the latter regimen. The trial commenced in March 1994 and is ongoing.

Methods: Standard dose CEP consists of cyclophosphamide 750 mg/m², epirubicin 75 mg/m², vincristine 1.4 mg/m² and prednisolone 100 mg/day for 5 days. The high-dose arm consisted of cyclophosphamide 1500 mg/m², epirubicin 150 mg/m² and vincristine, prednisolone and filgrastim. Cycles were given every 3 weeks to a total of 6 to 8. Cardiac function was evaluated by measuring the left ventricular ejection fraction (LVEF), pre-treatment, after 6 cycles and 6 months after completion of chemotherapy.

Results: There were 9 reports of cardiac toxicity on the high-dose CEP arm, reduced LVEF in 7 of 5 in clinical cardiac failure in 2. In the standard-dose arm, there were 8 reports of cardiac toxicity, all due to a fall in LVEF. No deaths due to cardiac toxicity have occurred in the study so far.

Conclusions: No increase in the incidence of cardiac toxicity is apparent on the high-dose arm of this study but longer follow-up is required to detect late cardiac effects of anthracycline therapy.

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STEM CELL AUTOTRANSPLANTATION IN RESISTANT OR RELAPSING AGGRESSIVE NON-HODGKIN LYMPHOMA PATIENTS: FACTORS ASSOCIATED WITH SURVIVAL


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Aim of the study: To analyze the role of prognostic factors in patients with resistant or relapsing aggressive non-Hodgkin lymphoma (NHL) who underwent high dose chemotherapy (HDC) supported by autologous hematopoietic stem cell transplantation (ASCT).

Patients and Methods: Since March 1989 to July 1998 75 patients (median age 50 years, range 16-66) from 6 Italian and 1 Swiss centers with resistant or relapsing large cell lymphoma (DLCL) were consecutively treated with high dose sequential therapy (HDS) (Gianni et al., 1997) (45pts), or DHAP salvage chemotherapy (30pts), followed by ASCT conditioned with BFAM (44pts) or high dose melphalan and midovantrone (HDMMA) (18pts).

Results: After a median follow-up of 12 months (2-109), 22 patients (29%) were in CR at 1 year, and 29% OS and 26% EFS at 3 years were 20%. The following prognostic factors were examined: age, gender, LDH vs DHAP, BEAM vs HDMMA, number of previous treatments, bulky disease, B symptoms, bone marrow involvement, and site of transplantation. Multivariate analysis showed that state at transplantation was the only variable associated with clinical outcome.

Conclusion: This analysis confirms that a more prolonged survival can be obtained in a proportion of resistant or relapsing DLCL patients provided they achieve a complete or partial remission before high dose chemotherapy and ASCT.

8. High Dose Therapy
EXPERIENCES WITH THE CYCLOPHOSPHAMIDE-ETOPOSIDE-PROCARBAZINE-PREDNISONE (CEPP) PROTOCOL AS A SAVAGE TREATMENT FOR RELAPSED OR REFRACTORY HIGH-GRADE NON-HODGKIN’S LYMPHOMA PATIENTS

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Introduction: Patients with high-grade NHL who do not achieve a complete remission (CR) after the initial treatment have poor prognosis. CEPP is the second-line relatively well tolerated regimen advised by Chao et al. in 1990 mainly for refractory or relapsed NHL patients. The rationale for CEPP is its use etoposide (VP 16) as an alternative to doxorubicin.

Methods: CEPP protocol was used in the proposed doses in every for weeks in 2-6 courses. From Jan 1991 60 pts were treated (35 men, 25 women, median age 61 years) with refractory (22 pts) or relapsed (38 pts) aggressive NHL after previous chemotherapy (40 pts) or radiochemotherapy (17 pts); one patient was irradiated only and two other was not previously treated. The response can be evaluated in 54 pts. The therapy was quite well tolerated, granulocytopenia was developed in one third of courses.

Results: 26 pts achieved remission (48%), 10 from them CR, 28 failed to respond. Median survival of pts with CR was 23 months and with PR 11 months. Fourteen responders were alive and only two out of the non-responders. Relapsing pts with intermediate or high-grade NHL had better response to CEPP than that of refractory NHL. These results compare favorably with other salvage regimens.

Conclusions: CEPP is advisable for pts who relapsed or cannot tolerate doxorubicin-containing regimens.

INFECTIONS IN PATIENTS MANAGED AT HOME DURING AUTOLOGOUS STEM CELL TRANSPLANTATION FOR LYMPHOMA AND MULTIPLE MYELOMA

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A group of 51 patients with multiple myeloma, non-Hodgkin's lymphoma or Hodgkin's disease receiving high grade chemotherapy and autologous peripheral blood stem cell transplants were reviewed for infections and clinical courses in the peri transplant period at this hospital. This group was compared with 85 cases with the same diagnoses, receiving the peripheral stem cell transplant as an inpatient in a high efficiency particulate air filtered bone marrow transplant unit.

Patients were treated at home based on choice, geographic accessibility, availability of an educated care giver and a clean home environment with comprehension of the concepts of infection and aseptic techniques.

Febrile neutropenia and sepsis were not increased in the home group and no episodes of serious septic shock was seen in this group. Patients at home received prophylactic oral ciprofloxacin and trimethoprimsulphadiazine during the phase when the absolute neutrophil count was <1x10^9/L. Fewer gram negative infections, but no diminution in gram positive infections nor in the rate of fever was seen in patients at home. Empiric therapy with a third generation cephalosporin, teicoplanin and tobramyacin was instituted in 14 patients who developed a fever greater than 38.5°C. Of this group of 31, 18 required admission to hospital, 12 because of febrile neutropenia which persisted or was considered unsuitable for management at home due to sepsis. neutropenia lasting 13 with febrile neutropenia remained home throughout, as did the 20 cases not developing neutropenic fever.

This study demonstrates that selected patients can safely be managed in their home environment with a reduced risk from febrile neutropenia or other septic complications following autologous peripheral stem cell support.

BUCCYP16 AND EARLY AUTOLOGOUS STEM CELL TRANSPLANTATION (ASCT) IN HIGH RISK FOLLICULAR NON HODGKIN LYMHPHOMAS (NHL)

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Follicular non Hodgkin Lymphomas (nHL) has dismal outcome and poor Disease free Survival (DFS) if age < 50 years, advanced stage, bulky disease or BM involvement are present at diagnosis. We investigated the use of HI-dose chemotherapy (HDC) and autologous stem cell transplantation (ASCT) as front line therapy in poor prognosis follicular nHL younger than 55y, 12 pts (median age 40y) in advanced stage follicular nHL (BM + 100%) and adverse prognostic factors as bulky (83%) LDH > 500U/L (66.6%) and B symptoms (58.3%) underwent ASCT at a median time from diagnosis to transplant of 6.5 months. Stem cell source was peripheral blood (PBSC) in all pts. First line chemotherapy was ProMACE-CytaBOM (4 cycles) and two cycles of DHAP for in vivo purging and stem cell mobilisation. Immunomagnetic negative selection was performed in 5 pts. All pts were in chemosensitive disease (Pr or sPr) before ASCT. At the moment 9 pts are in CR (75%) and 3 in PR (BM+). Median follow up from transplants is 315 days (range 73-850 d). One relapse occurred (6 months after transplant). No related treatment deaths, but 1 engraftment syndrome and 8 Grade I and II Graft-versus-Host occurred. Early intensive therapy with ASCT is feasible (no TRD) and highly effective in chemosensitive pts with high risk follicular nHL. More investigative program including prospective randomized trials are needed to assess the efficacy of HDC and ASCT in treatment of young pts with follicular lymphomas in early phase of treatment plan.

8. High Dose Therapy