13. Pediatric lymphomas II

RISK GROUP DEFINITION FOR TREATMENT OF MATURE B-CELL LYMPHOMA/LEUKEMIA IN CHILDHOOD: AN UPDATE OF TRIAL NHL-BFM 90.

In trial NHL-BFM 90 we investigated a system for stratification of therapy into 3 branches based on the levels of serum LDH (normal<400 U/l), and 2 additional factors: branch R1: completely resected; R2: not resected, abdominal primary or abdominal or stage III primary sides of abdominal 5 years disease were separated into different branches by LDH < or > 500 U/l after diagnosis.

To allow international comparison we used the following risk factors:

- Stage (I-IV)
- B-ALL status
- 5 years LDH level

The risk groups were defined as follows:

Group I: Stage I or II, B-ALL 
Group II: Stage III or IV, B-ALL 
Group III: Stage I or II, no B-ALL 
Group IV: Stage III or IV, no B-ALL

The risk factors were used to determine the treatment strategy for each patient.

B-CELL LARGE CELL LYMPHOMA IN CHILDREN. DESCRIPTION AND OUTCOME WHEN TREATED WITH THE SAME REGIMEN AS BURKITT.


Large cell lymphomas are more rare in children than Burkitt lymphoblastic and their treatment is still object of controversies: should they be treated as one entity or according to histo-immunological subtype? The latter attitude is the one adopted in the SFOP (French Society of Pediatric Oncology). B-cell large lymphomas are treated with the same regimen as Burkitt lymphoma.

In the LBM 89 study, 507 patients with B-cell neoplasia were registered in December 1995. Slides of 425 pts were centrally reviewed 47 had large cell lymphoma, generally centroblastoid, treated between July 1989 and April 1995. There were 23 boys and 15 girls. Age 1 to 16 years, median 12 years. Patients were classified as: 4 were stage IV, 20 adenopathy, 9 head and neck, 6 node, 5 bone, 1 extraluminal and 1 intracranial. Cytogenetics was successfully performed in 7 pts only. There were 7 cases (12%) in stage IV and 6 cases in stage I+IIA lymphoma. This level was below and above twice the upper limit of the normal value in 35 and 9 patients respectively, unknown in 3. Treatment intensity was adapted to risk groups: 13 pts received 1 and 7 pts were treated in group A with 2 polychemotherapy courses without CNS prophylaxis; 31 pts (8 other st I and II, 22 st III, 1 st IV, group B received 2 courses according to high dose (HD) methotrexate 500 mg/m^2, cyclophosphamide and Ara-C in continuous infusion: 4 pts (3 st IV) were treated in group C received 4 courses with higher dose methotrexate 8 g/m^2 and HD ara-C and VP16 in consolidation phase. There were 4 failures: 2 treatment related deaths and 2 relapses, 10 pts are currently in CR at 4 mo who have a median follow-up of 35 months (7-84). EFS is 89% ± 2 pts at a plateau at 32 months. In conclusion: B-large cell lymphomas represent about 10% of childhood B-cell lymphomas. There are more often localisation and with low level Burkitt. Extra-abdominal tumors are frequent. Treated with the same risk adapted polychemotherapy regimen as Burkitt, their outcome is similar and as good, but relapse can occur later. Supported by ARC.

DISSEMINATED NON-LYMPHOBLASTIC NON-HODGKIN'S LYMPHOMA (DLNHL) OF CHILDHOOD: A RANDOMIZED PHASE II TRIAL OF SHORT INTENSIVE TREATMENT
M. Cairo, M. Knoll, M. Morse, R. Hutchison, R. Harris, C. Kjeldberg, M. Kadin, E. Radel, L. Steinheutz, A. Meadows. Children's Hospital of Orange County, Orange California and Children's Cancer Group, Arcadia, California.

Children with DLNHL, especially those with high-risk (HR) BM and CNS involvement treated on previous CCG trials, had a uniformly poor prognosis (Anderson et al N Engl J Med 308:559, 1988; Chilote ASCO 10:249, 1991). Development of short intensive therapy for DLNHL demonstrated promising results (Patte et al ASCO 8:279, 1989). Therefore, CCG conducted a Phase II trial to determine the toxicity associated with the short intensive treatment regimen for children. C21 yr and DLNHL were randomized to the French (LMB) or German (R) regimen. The FR regimen consisted of COP induction, COPAD1 induction, and maintenance therapy. Patients with evidence of CNS disease (CNS+) received 1800 cgy, and total Ttx consisted of approximately 5700 cgy. 79 pts were randomized to OR (16 standard risk) and 41 to FR (23 high risk). The 2 treatments were significantly more toxic with respect to pancytopenia, 26% of pts had grade 2 hyperleukocytosis (p=0.05), and anti-fungal administration (p=0.01). FR was also associated with a significant increase in the days of hospitalization in course 1, 2, 3 (p=0.01). Estimated 5-year EFS and IC was 80% and 84%, respectively. For HR pts, the FR had a 24-mo EFS of 80% vs 61% for the OR (p=0.10). For SR pts, the OR was associated with a 24-mo EFS of 100% vs 90% for the FR (p=0.21). The FR was associated with a decreased 18-mo IC and large cell histology with compared with other histologies (30% vs 29%, p=0.036). Poor prognostic factors associated with a decrease in the 18 mo EFS included: BM >2.0 U/L and CNS positive at Dx (p=0.026 and p=0.0094, respectively). In conclusion, children with SR DLNHL treated with short intensive therapy had a 90-100% 24-mo EFS and HR had a 60-80% 24-mo EFS. These results are considerably improved from previous CCG DLNHL trials (CCG-003 [HR] 45% 2 yr EFS).

LARGE CELL ANAPLASTIC LYMPHOMA IN CHILDREN: experience of the SFOP EM 91 protocol.

Between February 1991 and September 1994, 46 patients newly diagnosed with a large cell anaplastic lymphoma (LCA) were enrolled in the H911 study. After a cytoreductive phase COP course (Vincristine 1 mg/m^2, Cyclophosphamide 300 mg/m^2, Prednisone) were administered 2 induction courses (COPADP) with high dose methotrexate (3 g/m^2 in 3) and ara-C (21 d). Cycles (DD12) and ara-C (21 d) and prednisone) were administered in the maintenance phase (CPAD1 inductions, COPAD2 induction, ara-C-CVP). Consistency, consolidation, and maintenance therapy. Patients with evidence of CNS disease (CNS+) received 800 cgy, and total Ttx consisted of approximately 5700 cgy. 79 pts were randomized to OR (16 standard risk) and 41 to FR (23 high risk). The 2 treatments were significantly more toxic with respect to pancytopenia, 26% of pts had 24-mo EFS and IC was 80% and 84%, respectively. For HR pts, the FR had a 24-mo EFS of 80% vs 61% for the OR (p=0.10). For SR pts, the OR was associated with a 24-mo EFS of 100% vs 90% for the FR (p=0.21). The FR was associated with a decreased 18-mo IC and large cell histology with compared with other histologies (30% vs 29%, p=0.036). Poor prognostic factors associated with a decrease in the 18 mo EFS included: BM >2.0 U/L and CNS positive at Dx (p=0.026 and p=0.0094, respectively). In conclusion, children with SR DLNHL treated with short intensive therapy had a 90-100% 24-mo EFS and HR had a 60-80% 24-mo EFS. These results are considerably improved from previous CCG DLNHL trials (CCG-003 [HR] 45% 2 yr EFS).

13. Pediatric lymphomas II
PERIPHERAL T-CELL LYMPHOMA OF CHILDHOOD AND ADOLESCENCE


13. Pediatric lymphomas II
Treatment of T cell lymphoma without cranial irradiation - UKCCSG

O.B. Eden, I. Hann, J. Messeon, C.R. Pinkerton on behalf of U.K. Children's Cancer Study Group

Between July 1990 and April 1995, 99 unselected children with T lymphoblastic lymphoma were treated according to an intensive 'leukaemia' protocol (5 drug induction, 2 intensification pulses at weeks 5 and 23, high dose i.v. methotrexate 6-8mg/M² with ongoing I/V methotrexate and two years of continuing therapy). In March 1992 daunomycin (90mg/M²) was removed from induction to reduce total anthracycline exposure to 180mg/M². There were: 9 Stage I, 3 Stage II patients (median age 90 months), experiencing only one event (a secondary AML) at 9-56 months follow up. There were 66 Stage III and 21 Stage IV patients with a median age of 90 months (2-189).

The 4 year EFS for Stage III and IV patients is 65% (95% C.I. 53-78). This result is not significantly better than in our previous protocol 8503, 71% (C.I. 61-80) and due almost totally to a greater proportion of and worse survival of Stage IV patients. There was a non-significant excess of CNS relapses in 9004, totally confined to Stage III with none in Stage IV despite no cranial irradiation. 10% of Stage IV, and 27% of Stage III were in C.R. at Day 28; by Day 60 57% of IV and 70% of III were in C.R. For those not in C.R. at Day 60 there was a 7X reduced survival. 9/21 aggressively treated early relapses are alive (none in 8503). Future therapy requires new approaches for non-remitters (Day 60).
14. Future developments

Bel-2 Antisense Therapy in Lymphomas: In vitro and in vivo Mechanisms, Efficacy, Pharmacokinetic and Toxicity Studies
F.E. Coates1, M. Carso1, P. Raynaud1, R. Orz1, C. Poole1, B. Bryer1, M. Harper1, A. Wehbe1, P. Catterall1, L. J. 1, J. D. Canning2, J. Wehbe1, D. Cunningham2, 3
1LRF Dept Haematology & Oncology, Institute of Child Health, London WC1N 1EH, UK, 2CRC Cancer Therapeutics, 3CRC Medical Unit, Royal Marsden Hospital, Sutton, Surrey, UK, 4GENTA, San Diego, USA

The majority of follicular lymphomas and some high grade lymphomas are associated with the (1p;18) translocation and deregulated expression of Bcl-2 gene. This leads to protection against chemotherapy induced apoptosis and a malignancy that is difficult to eradicate fully with current therapy. In vitro antisense oligodeoxynucleotides to Bcl-2 have demonstrated in phase 4 regulation of the gene in B-lymphoma cell lines and subsequent induction of apoptosis. Controls with sense and nonsense oligodeoxynucleotides had no effect on cell growth suggesting a specific specific effect. Having set up an in vivo SCID mouse model of the (1p;18) lymphomas using the Daudi and SU-D 4 cell lines, we have been able to demonstrate consistent anti lymphoma efficacy with Bel-2 antisense oligodeoxynucleotides. In preparation for a phase 1 human study we have investigated a number of parameters in order to determine the best candidate oligodeoxynucleotide sequence and chemistry. Both 18 and 20 mer full thorium AS oligodeoxynucleotides from the open reading frame consistently gave the greatest efficacy when infused subcutaneously over a 2 week period at a dose of 3mg/kg/day. Disease was eradicated in 83% of mice (50 mice treated with this AS). This compared to efficacy in 62% of mice treated with the same AS sequences but with only partial time limited glutathione protection. The 18 mer full thorium AS was chosen as the candidate molecule for the phase 1 Study (Anticoide G3139 molecule, Genta, USA). A dose escalation study established an efficacy dose relationship and extension of the treatment period to 3 weeks also resulted in eradication of lymphomas in all AS treated mice. Fluorescently labelled AS demonstrated good cellular internalisation of the molecule in both the nucleus and the cytoplasm. In vivo experiments to show a specific downregulation of Bcl-2 by the ASO revealed specific lowering of Bcl-2 expression within the lymphomas. Pharmacokinetics showed the ASO to be widely distributed with accumulation within the organs particularly kidney, liver, spleen, GI tract and bone marrow. IV administration had a plasma 1/2 life of 11hrs compared to 22 hrs SC and a tissue half life of over 24 hrs. SC administration at steady state gave a greater availability of parent compound compared to IV, suggesting this to be the preferable route of administration. Toxicity studies in mice resulted in death at doses of 30mg/kg/day and above. The cause of death was liver and myeloid marrow necrosis. The LD10 was established at 15mg/kg/day. Alternative backbones for the 3139 AS code have now been investigated together with liposomal delivery and may provide improved efficacy. We have established an antilymphoma effect in vitro and in vivo with the Anticoide G3139 molecule, investigated its possible mechanism of effect and have been able to establish parameters for a Human Phase 1 Bel-2 antisense trial in lymphoma.

NEW DRUGS FOR TREATMENT OF MALIGNANT LYMPHOMA
Susan G. Arbuck and Bruce D. Cheson, Cancer Therapy Evaluation Program, National Cancer Institute, Bethesda, MD 20892

Novel approaches are needed to improve the prognosis of patients with NHL. Recently, the purified analogs fludarabine and cladribine provided a major advance in treatment of low grade lymphomas. These agents produce responses in 50% of previously untreated patients, (10-15% CRs) and 65-88% of those who are previously untreated (approximately half CRs). 2-Aminoo-6-methoxypurine arabinoside (506U), another antitumorabolite, is a water soluble prodrug of ara G, which promises interim data have been reported in T-cell lymphomas and T-ALL. Other classes of active cytotoxic agents require further clinical evaluation. These include the topoisoaserase I inhibitors, irinotecan (CPT-11), topotecan and 9-aminoquinolinophosphoridines. Paclitaxel, a taxane, also appears to have some activity in heavily pretreated patients. Signal transduction modulators, such as bryostatin, which has had activity in low grade NHL in a phase I trial, are of interest. This protein kinase C modulator also induces differentiation, and decreased Bcl-2 expression in a lymphoma cell line. Preclinical and limited clinical data with suramin, a compound that antagonizes the binding of several polypeptide growth factor ligands with their receptors, and has effects on RNA polymerases, support the need for further study of this agent. The patient population available for study has implications for the development of targeted therapy for new agents. Patients with NHL often receive investigational agents in advanced stages after extensive prior therapy.

When prior therapy is limited to two regimens for low-grade disease and one for intermediate- to high-grade disease, as is it in NCI-sponsored trials, the availability of patients is limited. A variety of different and promising agents require efficient evaluation and warrants study in less heavily pretreated patients.

PHASE I BCL-2 ANTISENSE TRIAL: PRELIMINARY RESULTS
A. Wehbe1, D. Cunningham1, P. Cotter1, M. Hill1, P. Catterall1, F. di Stefano1, C. Viner1, J. Prendiville1, S. Rahal1, Z. Drewnowska2, The Royal Marsden Hospital and Institute of Cancer Research, Sutton, UK, 1Institute of Child Health, London1, UK and Genta Incorporated, USA.

The Bcl-2 protein is overexpressed in a number of tumours, including 85% of low grade follicular lymphomas and approximately 50% of intermediate high grade tumours where it is correlated with a worse prognosis. Dereegulation of the Bcl-2 gene results in increased protein levels and a subsequent resistance to programmed cell death (apoptosis). Antisense oligodeoxynucleotides are short single strands of DNA (usually 15-25 bases long) which have a sequence complimentary to a key region of the messenger RNA of the target gene. There is strong in vitro evidence that fully phosphorylated oligodeoxynucleotides complimentary to the open reading frame of the Bcl-2 messenger RNA results in a specific down regulation of the Bcl-2 protein leading to apoptosis. Using a scid mouse model, it was determined that an 18 mer fully phosphorylated oligodeoxynucleotide given as a two week subcutaneous infusion resulted in a potent antitumour effect. Rodent toxicity was similar to previous phosphorhibites and toxicity evaluation in 3 primate results in no deaths or treatment related clinical signs or laboratory abnormalities. This invivo and invitro data together with the low toxicity seen by other investigators using phosphorhibites enabled us to commence a phase I trial. This trial uses the 18-mer fully phosphorylated oligodeoxynucleotide (Anticoide G3139, material supplied by Genta Incorporated, USA) given as a subcutaneous infusion over a 2 week period, for relapsed non-Hodgkin’s lymphoma of any grade that over expresses the Bcl-2 gene on immunohistochemical analysis of pathological specimens. The primary endpoint of the trial is to establish the maximum tolerated dose but in addition response will be assessed using conventional CT criteria together with molecular analysis of blood, lymph nodes and bone marrow samples looking for a reduction in the level of the Bcl-2 protein. We will report the initial results of this clinical trial.


In a phase II clinical trial, we treated patients with refractory or relapsed NHL with single agent Taxol given at 200 mg/m2 IV 3 times. Treatment was repeated every 3 weeks. Responding patients received therapy for a maximum of 8 courses. Of 96 evaluable patients, 45 (47%) had primary refractory disease, and 51 (53%) had relapsed lymphoma. The median number of prior treatment regimens was 2 (range, 1-10 regimens). Response rates according to histologic diagnosis are:

<table>
<thead>
<tr>
<th>Histology</th>
<th>N</th>
<th>CR</th>
<th>PR</th>
<th>CR + PR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade</td>
<td>45</td>
<td>3</td>
<td>7</td>
<td>22% (11%-37%)</td>
</tr>
<tr>
<td>Intermediate</td>
<td>44</td>
<td>7</td>
<td>6</td>
<td>30% (17%-45%)</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>7</td>
<td>0</td>
<td>1</td>
<td>14% (0.4%-58%)</td>
</tr>
<tr>
<td>Total</td>
<td>96</td>
<td>10</td>
<td>14</td>
<td>25% (17%-35%)</td>
</tr>
</tbody>
</table>

Patients with relapsed lymphoma had a higher response rate than those with primary refractory disease (19/51=37% vs. 2/45=11%; P<0.01), and patients with relapsed intermediate grade lymphoma had a higher response than those with relapsed low grade lymphoma (9/19=50% vs 10/32=31%). In a subsequent trial, 30 patients with intermediate grade NHL were treated with Taxol (150 mg/m2/72 hour continuous infusion) + Cytoxan (900 mg/m2/d: days1-3) + Filgrastim (5ug/Kg/daily until ANC 2.10000),. The overall response rate to 27 eligible patients was 56% (33% for refractory and 73% for relapsing disease). We conclude that Taxol is an active new drug for the treatment of non-Hodgkin’s lymphoma. The activity of Taxol combination programs are currently under investigation with encouraging early results.

32

Expression of the mdr gene may be an important cause of chemotherapy failure in patients with NHL. ONCEP (Vincristine (O), Novantrone (N), Cyclophosphamide (C), Etoposide (E), and Prednisone (P)) chemotherapy contains three MDR-related agents (O, N, E) and was designed for studies of MDR modulation. PSC 833 is a non-immunosuppressive cyclosporine with greater in vitro MDR modulating activity than Cyclosporin A. Between February 1995 and February 1996, 15 patients (pts) with relapsed or refractory NHL received PSC 833 (5 mg/kg/d for 15 doses every 4 days (d) 1-4) and ONCEP (O 1.0 mg, N 3.0 mg/m², and C 650 mg/m² intravenously (iv) d 2; E 30 mg/m²/iv d 2-4; P 40 mg/m²/orally d 2-11). Doses of O, N and E were reduced 3-fold to account for the pharmacokinetic effects of PSC 833 on these MDR-related agents. Histologies included diffuse large cell, 9; diffuse mixed, 1; immunoblastic, 1; mantle cell, 3; small noncleaved, 4. Four pts had disease refractory to induction therapy. Five pts are currently in 3-23 month remission. Eight pts relapsed within 12 months of prior chemotherapy. Of 34 cycles of ONCEP-PSC, 10 were associated with Grade IV neutropenia (2 with fever), 8 with Gr III neutropenia, and 1 each with Gr III and Gr IV thrombocytopenia. Fifteen cycles were associated with Gr II ataxia (unsteady gait) and 1 with Gr III (inability to walk without assistance). In all cases, ataxia resolved within hours of completing PSC 833 doses. Two pts developed atrial fibrillation, and 3 pts had severe constipation. Of 12 evaluable pts, 2 achieved a complete response, and 5 achieved a partial response or minimal disease after 2-3 cycles of ONCEP-PSC. Four of the responding patients have subsequently received high dose therapy with autografting. ONCEP-PSC chemotherapy is well tolerated and has a significant activity in patients with recurrent or refractory NHL.

TREATMENT WITH CONCURRENT 2-CHLORODEOXYADENOSINE (CDA) AND INTERLEUKIN-2 (IL-2) FOR LOW GRADE B-CELL MALIGNANCIES AVOIDS CDA-RELATED LYMOPHENIA: A PILOT STUDY.

The group reported Hodgkin's disease (HD) as a possible candidate for IT use. The major reason for the high susceptibility of HD to treatment in the expression of lymphocyte activation markers such as CD25 or CD30 in very high copy numbers on Hodgkin and Reed-Sternberg (HS) cells. From a variety of many of 60 constructs evaluated, the most potent IT, RFT5.dgA (CD25), was as effective as unmodified ric against HS in vitro and destroyed more than 60% of solid HS tumors in nude mice. In addition, RFT5.dgA abolished the growth of disseminated human Hodgkin's tumors in a SCID mouse model. Thus, RFT5.dgA was selected for a phase-I clinical trial in patients with refractory Hodgkin's lymphoma. 15 heavily pretreated patients with end-stage, refractory HD were included. The IT was administered at total doses of 2, 10, 15, or 20 mg/m². Single doses were reduced to the vascular leak syndrome response. IT was effective in decreasing serum albumin, edema, weight gain, hypoalbuminemia, tachycardia, myalgia and weakness. Results included 2 PR, 4 SD and 9 PD. The maximal tolerated dose was reached at 15 mg/m². This study is being continued in phase II.
CLEANING OF BCL-2 (14:18) FROM PERIPHERAL BLOOD (PB) AND BONE MARROW (BM) IN PATIENTS (PTS) WITH RELAPSED LOW-GRADE OR FOLLICULAR (IWF-A-D) LYMPHOMA (NHL) FOLLOWING SINGLE-AGENT THERAPY WITH THE CHIMERIC ANTICD20 ANTIODY (MAB) IDEC-C2B8.

J Rogers, J Jackson, J Rosenberg, C Varela, J Leonard, AJ Grillo-López. IDEC Pharmaceuticals Corp., San Diego, CA, USA.

The bcl-2 translocation (14;18) is detected in lymphoma cells in PB and BM in the majority of pts with low-grade NHL. PCR based assays can detect 1 in 10 E-5 cells. Thus, this marker is useful in the detection of minimal residual disease. Intensive combination chemotherapy rarely results in clearance of bcl-2 in low-grade NHL and usually only in PB. There are few reports of BM clearance. The best results are in pts treated with methotrexate therapy, ex vivo marrow purging and ABMT where about 50% will clear both PB and BM. These pts have been shown to have a significantly longer disease-free survival and overall survival. We have developed a chimeric anti-CD20 MAB (IDEC-C2B8) that binds to lymphoma cells with an apparent affinity of 5 x 10^6 M. Single-dose Phase I clinical trials (PI CT) (Muloney, et al., Blood 1994;84:2457) have shown IDEC-C2B8 to be safe and well tolerated. Multiple-dose PBCT (Muloney, et al., Blood 1995;90(10):544) and chemotherapy combination PI CT (Cracon, et al., Blood 1995;95(10):554) have shown activity in pts with relapsed IWF-A-D NHL. In this study, IDEC-C2B8 was given in combination with CHOP chemotherapy. Interestingly, all bcl-2 (PCR) positive pts completing treatment (N=5) were reported to have converted to PCR negative (NEG) in blood and marrow. A multicenter, pivotal PBCT is currently underway in the United States and Canada in pts with relapsed IWF-A-D NHL where treatment consists of weekly x 4 IV infusions of IDEC-C2B8 at 375 mg/m^2. Genomic DNA obtained from PB and BM pts enrolled in this trial is being tested for the bcl-2/JA (14;18) by means of a nested PCR assay (Rogers, et al., Pro. AACR 1996) which detects the translocation in both the major breakpoint region and minor cluster region (sensitivity of 1 in 10^5 cells). Baseline PB and BM samples were tested in 73 pts: 32 (44%) were positive and 23 of 32 (72%) became NEG in PB prior to the 4th infusion. Follow-up (2 to 4 mo.) samples are available on 18 pts and 13 of 18 are still NEG in PB. BM samples are available in 11 of these pts and 6 are NEG. For pts with IWF-A-D NHL, bcl-2 status post-therapy has prognostic value and is known to serve as a marker of residual disease. Thus, the clearance of IDEC-C2B8 positive cells observed in these pts suggests that treatment with IDEC-C2B8 has significantly reduced tumor burden in PB and/or BM.

STAGE IV LOW GRADE LYMPHOMA (LGL): RANDOMIZED TRIAL OF TWO INNOVATIVE REGIMENS, WITH MONITORING OF BCL-2 BY PCR.

P McLaughlin, F Cabanillas, A Younes, MS Lee, MA Rodriguez, FB Hagemeister, A Sarris, A Preti. M.D. Anderson Cancer Center, Houston, TX, U.S.A.

We have previously reported encouraging response rates in LGL, in the salvage setting, with fludarabine, mitoxantrone, and dexamethasone (FND) (JCO 1994; 12:575; and JCO 1995, in press). Since 1992 we have conducted a front-line randomized trial comparing FND, followed by interferon, with our previously reported 11-drug ATT regimen (Ann Oncol 1994; 5 (sup 2): S73). We report here on the first 62 evaluable patients, registered through 12/94. In addition to standard endpoints of complete remission (CR), failure-free survival, and survival, we also determined molecular remissions by PCR for bcl-2 gene rearrangement in peripheral blood (PB) and bone marrow (BM) of follicular lymphoma patients. Preliminary results are as follows: bcl-2 Reversion To Negative

<table>
<thead>
<tr>
<th>Arm of Randomized Trial</th>
<th>No. of Patients</th>
<th>% CR</th>
<th>PR(3%)</th>
<th>PR(6%)</th>
<th>IM(3%)</th>
<th>BM(6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FND</td>
<td>31</td>
<td>77</td>
<td>8(0)</td>
<td>59</td>
<td>4(0)</td>
<td>2(0)</td>
</tr>
</tbody>
</table>

Additional PCR data will be forthcoming as batched samples are run.

Infectious toxicity has been twice as common in the 11-drug arm; other toxicities have been modest. To date, there have been only 4 deaths (1 toxic), and 14 relapses. While it is too early to formulate final conclusions, we note: (1) FND achieves high rates of CR, and can produce molecular remission; (2) the previously reported activity of the ATT regimen, including the achievement of molecular remission, appears to be verified; (3) serial monitoring of PCR data may permit a correlation between rapidity of attaining molecular remission and durability of clinical remission (Cabanillas et al, Blood 1995; 86 (sup 1): 604a); (4) if the outcomes are comparable in each arm, the less toxic regimen would be judged preferable.

FLUDARABINE (FLU) COMBINATIONS IN THE MANAGEMENT OF CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL) AND LOW GRADE LYMPHOMA (LGL)

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FLU is a major drug in low grade lymphoproliferative disorders. High response rates are noted in both CLL and LGL. FLU is a potent inhibitor of repair of DNA damage caused by radiation, and drugs such as mitoxantrone (M), cisplatinum (P), and cyclophosphamide (CYT). FLU enhances the formation of the triphosphate form of cytosine arabinoside (ara-CYT). Both FLU and ara-C have sensitized DNA-platinum adduct repair. The PIIFA regimen was developed to utilize this interaction in the management of refractory CLL and responses have been noted in Richter's transformation and lymphoplasmacytic leukemias. Over the last ten years at MDACC, we have conducted a number of clinical trials of FLU as a single agent in CLL and LGL. The results for FLU are compared in the table with FLU combined with prednisone (P), M, CYT, and PI + ara-C (PIIFA).

<table>
<thead>
<tr>
<th>Prior</th>
<th>FLU</th>
<th>FLU (5D)</th>
<th>FLU+P</th>
<th>FLU+M</th>
<th>FLU+CYT</th>
<th>PIIFA</th>
<th>FLU+ DOX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rx</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>--</td>
<td>76(82)</td>
<td>119(89)</td>
<td>36(78)</td>
<td>8(100)</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>+</td>
<td>78(58)</td>
<td>170(52)</td>
<td>14(57)</td>
<td>4(75)</td>
<td>3(33)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>13(46)</td>
<td>27(37)</td>
<td>13(85)</td>
<td>26(19)</td>
<td>20(60)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ref</td>
<td>--</td>
<td>16(13)</td>
<td>12(33)</td>
<td>7(28)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

In LGL, a response rate of 39/53 (69%) was noted in LGL with FLU. FLU and M with dexamethasone (FMD) in LGL resulted in a 48/51 (94%) response rate in previously treated LGL with 47% CRs. The improved results with FMD in LGL did not occur in CLL. In CLL, FLU/CYT has the highest response rate of any regimen in all patient groups. Significantly greater cytoreduction occurs with the FLUCYT regimen than FLU alone. Further exploration of the impact of FLU with DNA active agents in CLL, LGL, and even higher grade lymphomas should translate into clinical benefit for these patients.