success with RT only. One pt that refused further RT, died, with relapse, after radical surgical excision. The 2 pts with eyelid lesions were in DFS for more than 13 months. They were treated with RT. CH, as initial treatment after RT, has been done in one of our last pts that had lachrymal gland lymphoma because the MR after RT showed perhaps residual disease.

We conclude that surgery, if done, must always be followed by local RT. Local RT provides a good and almost permanent local control of the disease. Doses of 30–35 Gy controlled our low grade lymphomas with no late complications, when good shielding of the lens of the eye is possible. The prognosis for pts with small-cell lymphoma in the ocular adnexa seems difficult to predict, mainly for the orbit.

The role of adjuvant Ch with CVP or CHOP-like regimen, after local RT need to be investigated for pts with bad prognosis factors as retro-orbital lymphoma, bulky tumour and high grade malignancy histology.

810 PUBLICATION

DEXAMETHASONE, ETOPOSIDE, IFOSFAMIDE AND CISPLATIN AS SECOND-LINE CHEMOTHERAPY IN INTERMEDIATE OR HIGH GRADE NON-HODGKIN'S LYMPHOMA

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The combination of dexamethasone, etoposide (VP-16), ifosfamide and cisplatin (DVIP) was evaluated as a second line after adriamycin-containing combinations in intermediate or high grade non-Hodgkin's lymphoma (NHL). 39 patients (pts) (median age 68 years) entered the study. Objective responses were seen in 29 pts (74%) and included complete response (CR) in 14 (36%). Median duration of CR was 12 months (mos) and that of partial response was 3.5 mos. 13/25 (52%) pts who responded with CR to adriamycin-based combinations responded with CR to DVIP (vs 1/14 who failed to respond with CR). Durable remissions (24 ± 57+ mos) continue in 4 pts who responded with CR to front-line therapy. Main toxicity was myelosuppression. Median WBC nadir was 1100/mm^3 and median platelets nadir was 66,000/mm^3. There was no treatment-related mortality. We conclude that DVIP is an effective second line in histologically aggressive NHL, associated with acceptable toxicity, and has a curative potential in pts with relapsing disease.

811 PUBLICATION

SEQUENTIAL HIGH-DOSE THERAPY OF ADULT ACUTE LYMPHOBLASTIC LEUKEMIA

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We have developed a sequential treatment strategy for intensive post-remission management of adult ALL. Patients ⩾ 15 y in CR1 receive melphalan (200 mg/m^2) followed by peripheral blood stem cells mobilized with G-CSF (Neupogen, Amgen). On hematologic recovery, 2-year maintenance chemotherapy with daily 6-MP and weekly MTX is started. In case of relapse, an allograft is performed with etoposide (60 mg/kg) and TBI (1050 cGy) in CR2. 13 patients (6 M, 7 F; 32 y, 19–58) underwent PBSCT between 1/93 and 6/94. Toxicity of PBSCT was minimal with 2 d (0–5) of fever and 18 d (17–23) in hospital. Neutrophils reached 0.5 × 10^9/L on d 15 (12–27), and platelets 50 × 10^9/L on d 16 (12–77). 6-MP was started in 12 patients on day 32 (15–132). The median dose of 6-MP tolerated, averaged over the entire post-PBSCT follow-up period, was 45.4 mg/m^2/d. 10 patients (76.9%) are alive and well on chemotherapy in first CR at 18 mo (8–26). Of 3 patients relapsing at 4–7 mo, 2 are alive and well 7 and 8 mo after BMT from HLA-matched siblings in CR2. The third declined ABMT in CR2 and died of relapsed disease. We conclude that melphalan-PBSCT and maintenance chemotherapy have minimal toxicity and significant anti-leukemic activity in adult ALL, and patients relapsing after PBSCT can be salvaged by a second BMT with acceptable toxicity.

812 PUBLICATION

NON-HODGKIN'S LYMPHOMA OF INTERMEDIATE DEGREE. 13-YEAR FOLLOW-UP OF 89 PATIENTS TREATED WITH CHOP

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From January 1981 to January 1993, 89 patients with non-Hodgkin's lymphoma of intermediate degree were treated with 6 courses of CHOP chemotherapy. The median age of these patients was 57 years and male/female ratio was 1.53. 8 of the patients were large-cell follicular lymphomas, 33 diffuse small-cell, 25 diffuse mixed and 22 diffuse large-cell. The lymphatic areas most affected were: para-aortic 16%, left cervical 14%, right cervical 13% and mesenteric 11%. The number of lymphatic areas affected were: 1 (31%) 2 (29%) and 3 (16%). 24% of the patients were Stage I, 19% Stage II, 17% Stage III and 28% Stage IV. Bulky disease was present in 19% of the patients. The extra-nodal localizations most frequently affected were: Waldeyer ring 22%, followed by Spleen, Liver and Bone. Marrow with the percentage in each been 11%. 70% CR was achieved and 12% PR. More than 50% of the patients have had more than an 8-year follow-up and the disease-free survival rate at 13 years is 32%. A multivariant analysis, according to histological degree, primary localization and stage, will be presented.

813 PUBLICATION

TREATMENT OF PH+ CHRONIC MYELOGENOUS LEUKEMIA (CML) WITH INTERFERON ALFA 2B R(IFN)

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In 1988 and 1990 2 randomized IFN-based (Intron A, Schering Plough) pilot trials on CML were activated. The first trial (20 untreated pts, 18 evaluated, follow-up 56 months range 10–80) compared IFN versus IFN + cytoreductive chemotherapy to evaluate time to hematological/cytogenetic responses (HR, CR), event -free/overall survivals (EFS, OS); all pts received IFN for maintenance. Except for slight advantage in time to HR (P = NS) in low risk pts (compared to intermediate/high risk), no difference was observed between arms in CR/EFS/OS. Two low risks pts (1 from each arm) are currently BCR-ABL (−) (PCR) at 50/61 mos f-up. The second trial (23 untreated pts, 20 evaluated, f-up 44 mos range 7–59) compared 5 versus 3 days-a-week IFN maintenance after daily IFN until HR, to evaluate the impact on CR, EFS, OS. Four low risk pts (3 with IFN 5 days-a-week) remain BCR-ABL (−) at 22, 39, 45, 49 mos f-up (2 pts no current therapy). Six hematological relapses (3 in each arm) occurred in 2 intermediate, 4 high risk pts. Pts at low risk under IFN 5 days-a-week showed better CR and survived longer (median survival not achieved at 42 mos f-up), than intermediate/high risk pts. Side effects and toxicity did not limit therapy with IFN. According to these data, IFN at higher doses during induction/maintenance induces sustained HR and CR in low risk Ph+ CML pts. On this basis, in 1993 a new stratified multicentric (GATLA) trial (IFN at higher dose plus more intensive chemotherapy for induction/maintenance) was activated.

814 PUBLICATION

PERIPHERAL BLOOD TRANSPLANTS FOLLOWED BY MAINTENANCE INTERFERON IN MYELOMA

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Between November 1992 and November 1994, 73 myeloma patients were treated with high dose Melphalan (200 mg/m^2) followed by rescue with peripheral blood stem cells. All patients had received induction treatment with C-VAMP until maximum response. 24 patients were newly diagnosed while 49 patients had received some form of previous treatment. Response and engraftment details are shown in the table below.

	New Pts (24)	Previous treatment (49)	P value
Response			
CR	13 (55%)	11 (23%)	0.007
PR	9 (37%)	20 (40%)	NS
NR	2 (8%)	15 (31%)	0.03
Died	0 (0%)	3 (6%)	
Engraftment			
Pits 25 × 10^9/l	14 days	17 days	0.004
Neuts 1000/L	24 days	34 days	0.002
Inf start (Med)	55 days	68 days	0.017

The overall survival by the Kaplan Meier estimate at 2 years is 79.3% with a median follow up of 7.75 months and the progression free survival is 58% in the whole group of 73 patients. Interferon (inf) maintenance was started at a median of 61 days in 58/73 patients. We therefore conclude that the previously untreated group is a better risk group with respect to achieving remission as well as rapid engraftment. Inf was also started earlier in the untreated group. Longer follow up will be required however to comment on the efficacy of PBSCT. A CR rate of 55% in previously untreated patients is lower than our previously reported CR rate with ABMT in a comparable group of patients and the possibility of contamination of the stem cell grafts with myeloma should be borne in mind.

815 PUBLICATION

CA-125 SERUM LEVELS SIGNIFICANTLY CORRELATE WITH PROBABILITY OF RESPONSE IN MALIGNANT LYMPHOMAS

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Aim: to determine whether CA-125 serum levels correlate with disease extension and prognosis in patients with malignant lymphoma.

Methods: Ca-125 serum levels were assessed by using the OC 125 monoclonal antibody before treatment in 53 consecutive patients with malignant lymphoma (41 NHL/12 HD) and no sign of concomitant chronic hepatic disease.

Results: Increased serum levels (> 30 IU/ML) were observed in 27/53 (51%) pts. A significant difference between NHL (22/41) and HD (5/12) was not found. To date, 42 pts. are evaluable for response after the third cycle of chemotherapy. Basal abnormal CA-125 serum levels were associated with a significantly lower major response rate (14/22 vs 19/20; $P = 0.015$). At multivariate logistic analysis, presence of extranodal involvement was the only independent variable predictive of response. A further statistical estimation was made by considering a different cut-off for CA-125 (> 100 vs ⩽ 100). Only 2 of the 8 pts. with > 100 IU/ml CA-125 serum levels showed major responses, as compared to 31/34 responses in the other group ($P = 0.0004$). At logistic analysis CA-125 serum level > 100 IU/ml was the only parameter which significantly correlated with a lower response-rate ($P = 0.03$).

Conclusions: abnormal CA-125 serum levels are present in a significant rate of patients with malignant lymphoma. Our preliminary results show that very high serum levels (>100 IU/ml) correlate with a lower probability of response.

816 PUBLICATION

DEVELOPMENT OF AN ACTIVE CHOP-MODIFIED REGIMEN WHICH ALLOWS MORE CONTINUOUS AND BETTER TOLERATED TREATMENT FOR DIFFUSE AGGRESSIVE NON-HODGKIN'S LYMPHOMAS (NHL)

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A CHOP-variant regimen was developed in order to allow administration of full-doses therapy with reduced gastrointestinal and neurologic toxicity. The traditional CHOP regimen was modified as follows. Adriamycin 25 mg/m^2 iv day 1 and day 8, Cyclophosphamide 500 mg/m^2 iv day 1 and day 8, Vincristine 1.2 mg/m^2 iv day 1 and day 8, Prednison 50 mg/m^2 po days 1–8. Vincristine doses did not exceed 2.0 mg. The regimen was repeated every 21 days for 6–8 cycles. This schedule, allowing a more continuous treatment, would also adopt some of the basic concepts of the 2nd and 3rd generation regimens. Between March 1989 and March 1995 42 patients (age 25–84 yr) with stage II–IV diffuse aggressive NHL (Working Formulation F, G, H) were treated with acceptable toxicity. Most patients had grade 2 leukopenia and/or thrombocytopenia. No platelets transfusions were needed and the use of growth factors (G or GM-CSF) was not required. No life-threatening infections and no toxic deaths were observed. The regimen was safely administered also in elderly patients (17 patients had > 70 years). The large majority of patients experienced only mild nausea and vomiting. All patients had grade 3 alopecia.

The overall response rate was 85% (56% CR and 29% PR). Actuarial 3-years failure free survival is approx. 45%. These results appear to superimpose those achieved in the SWOG/ECOG trial (Fisher *et al.* NEJM, 1993).

This regimen therefore represents a CHOP variant that retains efficacy and appears easier to be administered especially in elderly patients.

Radiobiology

817 ORAL

TIME COURSE OF RADIATION-INDUCED APOPTOSIS IN THE ADULT RAT SPINAL CORD

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Radiation-induced apoptosis has been reported in thymic, lymphoid and hematopoietic cells but is infrequently documented in other adult mammalian cell types. In this study, we examined the time course of radiation-induced apoptosis in the adult cervical rat spinal cord following a single dose of 8 or 25 Gy. Apoptosis was assessed by morphological criteria under light and electron microscopy, and immunohistochemically in-situ using ApopTag to detect 3'-OH ends of DNA fragments. Little evidence of apoptosis (0.3 ± 0.3 apoptotic nuclei/spinal cord section) was observed in control un-irradiated spinal cord. A significant increase in the number of apoptotic cells was seen at 4 hr, the number peaked at 8 hr (53.7 ± 3.5 per spinal cord section after 8 Gy, and 60.7 ± 8.7 after 22 Gy) and returned to the baseline level by 24 h. A dose of 22 Gy induced apoptosis than 8 Gy at 4, 6, 10 and 12 h ($P < 0.006$), but not at 8 h. More apoptosis was observed in white matter (79 ± 3%) than in gray matter (21 ± 3%). All the apoptotic cells were observed in GFAP negative glial cells and none in vascular endothelial cells and neurons. We conclude that apoptosis in glial cells may represent a biologically relevant mechanism of radiation induced cell kill in the central nervous system. (Supported by NCIC.)

818 ORAL

RELATIONSHIP BETWEEN P53 CONSTITUTIVE/INDUCED LEVELS AND CELLULAR RESPONSE TO RADIATION

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The inhibition of replicative DNA synthesis, in which p53 has a pivotal role, is an important component of the cellular response to radiation-induced DNA damage. In this study we have examined the relationship between p53 levels before and after irradiation, radiation-induced cell cycle delays and radiosensitivity in a panel of 8 human tumour cell lines.

The cell lines differed widely in their clonogenic survival after radiation, (SF2 = 0.18–0.82). Constitutive p53 protein levels varied from 2.2 ± 0.4 to 6.3 ± 0.3 OD units per 10^6 cells. p53 after irradiation (6 Gy) also varied among the cell lines, ranging from no induction to a 1.6 fold increase in p53 levels 4 hours after treatment.