Methods: We have treated 10 pts. with UM, less than 10 mm height, without evidence of metastases. Preliminary dosimetry was performed with BEBIG program. COMS plaques diameters was 14–22 mm (2 mm margin tumor). The dose was always referred to tumor apex. Average: dose was 88 Gy, dose rate 80 cGy/h. Surgical implant was made in the brachytherapy theater under general anesthesia. After to open yuxtacorneal conjuntiva, transilumination exploration and previous sutures was performed and definitive implant placed. In 9 cases was necessary to remove the rectus m. Minimal follow up: 6 months.

Results: Tolerance was good. Acute conjuntivitis was normal and controled with topical treatments.

Conclusion: Epiescleral I. 125 plaques is elective conservative treatment for UM. Brachytherapy is feasible. More follow up and number of pts. is necesary to know local control rate and late effects.

1176 PUBLICATION

RT-PCR detection of melanoma cells in peripheral blood stem cell harvests of patients with metastatic malignant melanoma

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The objective of this study was to develop a sensitive multimarker polymerase chain reaction assay to detect melanoma cells contaminating peripheral blood stem cell harvests (after G-CSF 2 × 5 μg/kg daily times; 4–5 days) of patients with progressive metastatic malignant melanoma. The melanocyte-specific transcripts of tyrosinase and Melan-A/MART-1 as well as the tumor-specific transcript of Mage-3 were used as molecular markers to detect neoplastic cells in eleven metastatic malignant melanoma patients to be treated with high-dose chemotherapy and autologons peripheral stem cell support (Table).

Table: Patient characteristics and results

Patient	Sex/Age (yr)	RT-PCR results: Tyr/MART-1/Mage-3	Metastatic Sites
A	f/27	−/−/−	ST, bone
B	m/26	−/−/−	cutaneous, lymph, pulm
C	m/55	−/−/−	ST, lymph
D	m/47	−/−/−	pulmonary (bulk)
E	m/45	−/−/−	pulm, lymph, liver
F	f/48	−/−/−	lymph, liver, SC
G	m/25	−/−/−	SC, pleural, lymph
H	f/39	−/−/−	lymph
I	m/38	+/−/+	lymph, liver, spleen
J	f/43	−/−/−	lymph, SC
K	m/35	−/−/−	lymph, liver

ST = soft tissue, SC = subcutaneous, lymph = lymphatic, pulm = pulmonary, Tyr = tyrosinase.

With a sensitivity of the nested tyrosinase reverse transcriptase-polymerase chain reaction (RT-PCR) method to detect one melanoma cell in 2 × 10^6 peripheral blood mononuclear cells, only one patient's stem cell harvest tested positive for tyrosinase and Mage-3 message. All harvests were negative for Melan-A/MART-1, which result may be due to a ten-fold and five-fold lower sensitivity of detection when compared to tyrosinase RT-PCR and Mage-3 RT-PCR, respectively. Our results suggest that melanoma cells usually are not mobilized into peripheral blood to a significant degree following G-CSF application

1177 PUBLICATION

Metastatic ocular melanoma – Experiences with chemoimmuno-/polychemotherapy

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Purpose: At the Dept. of Dermatology, University of Heidelberg, between 1991 and 1996 32 patients (pts.) (14 females, 18 males, median age 55 years) with ocular melanoma were seen. 30 pts. had uveal and 2 conjunctival melanoma. 8 of 32 pts. (25%) are free of disease for 34 months (mo.) median, 24 pts. progressed and most developed multilocular metastases e.g. in liver (87.5%), subcutaneous tissue (33.3%) and lymph nodes (20.8%). In 7 pts. liver metastasis represented the only site of metastatic disease.

Methods and Results: 21 pts. with metastatic disease either received chemoimmunotherapy with Dacarbazine (DTIC) and Interferon α (IFN) or polychemotherapy consisting of DTIC, Cisplatin and Vindesine (DVP). DTIC/IFN was given to 13 pts.. No complete or partial responses (CR, PR) could be obtained. Stable disease (SD) lasting 3.5 mo. was achieved in 4 pts. Median survival of first line treated pts. was 9 mo. and of pretreated pts. 6 mo.. DVP was given to 13 pts., neither CR, PR or SD could be achieved. Median survival of first line treated pts. was 6 mo. and of pretreated pts. 4 mo..

Conclusion: These results once more demonstrate that therapeutic concepts that can achieve response rates of up to 53% in metastatic *cutaneous* melanoma are of little benefit in metastatic *ocular* melanoma.

1178 PUBLICATION

Oral etoposide in patients (pts) with Kaposi's sarcoma (KS)

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Purpose: Etoposide (E) has been used in the treatment of a wide variety of neoplasms, including KS. The best therapeutic approach is still unclear. We herein report the preliminary results of a phase II trial of oral E in generalized and progressive Kaposi's Mediterranean sarcoma (4 pts) and KS developed under immunosupressive therapy (4 pts).

Methods: Between September 1993 to March 1996, 8 patients (pts) with biopsy confirmed progressive KS were accrued. All pts were HIV (−). Median age was 43 yrs (range 31–67). Five pts had received prior treatment; with RT (3), RT and chemotherapy (1) or chemotherapy (1). 3 pts had renal transplantation and 1 pt had pemphigus vulgaris. All pts had stage II disease. Oral E was given at the dose of 50 mg bid for 10 days every 21 days. All pts completed at least 2 cycles, 6 pts received more than 4 cycles (range 2–9). During E treatment pts with renal transplantation had been using azathioprine and prednisone.

Results: In three pts with renal transplantation, grade III neutropenia were developed. No other grade III and IV toxicities were detected. Of the 8 pts, 1 pt required dose reduction of 25% and 2 pts delay of at least 1 week due to hematological toxicity (in pts with renal transplantation). 7 pts achieved a complete response (87%) which continue for 3, 8+, 8+, 11+, 14+, 18+, 29+ months, respectively. After completing chemotherapy all these 7 pts are still alive. In 1 pt with previous chemotherapy and renal transplantation minimal regression was detected. This pt died 4 months after completion of chemotherapy because of a cardiac reason.

Conclusion: In pts under immunosupressive therapy, main toxicity is hematologic. It may be concluded that oral E is effective for use in pts with generalized and progressive Kaposi's Mediterranean sarcoma or KS developed under immunosupressive therapy.

Lymphomas

1179 ORAL

Clinical activity of the monoclonal antibody (MAB) IDEC-C2B8 in patients (pts) with relapsed low-grade or follicular NHL (R-LG/F NHL)

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Purpose: We conducted a single-agent, multicenter, clinical trial (PIII) in a total of 166 pts with R-LG/F NHL (IWF classes A, B, C, D), treated with IDEC-C2B8 at 375 mg/m^2 weekly for 4 infusions to establish safety and efficacy of the MAB.

Pt characteristics: Gender – 61 F/105 M, median age – 57 years, median time since diagnosis – 4.1 years, stage at diagnosis – 78% III/IV, prior chemotherapy – median 2 relapses.

Results: Adverse events (AEs) were primarily related to 1st infusion and usually consisted of fever, chills, nausea, and headache. Only 34 pts had grade 3, and five pts had grade 4 treatment-related AEs (usually transient and reversible). There were no treatment-related deaths. Incidence of HACA was <1% and not associated with AEs. In the 166 pts, the overall response rate (ORR) was 48% (6% CR and 42% PR). Evaluable pts (151/166) had an ORR of 50% (6% CR and 44% PR). Responses (CT scans) were confirmed (blinded audit) by an independent panel of lymphoma experts (LEXCOR panel) using established response criteria. Median time to progression for responders has not been reached (9+ mo median follow-up). The ORR in

pts resistant to first, last, or all chemotherapy were 43%, 34%, and 32% respectively. In 23 pts relapsed after ABMT the ORR was 78%.

Conclusions: IDEC-C2B8 is well tolerated and does not impair marrow reserves. Thus, subsequent chemotherapy is not precluded. Outpatient therapy is feasible and is completed within 22 days (days 1, 8, 15, and 22). IDEC-C2B8 is safe and effective in the treatment of pts with R-LG/F NHL.

1180 ORAL

First demonstration of anti-lymphoma activity of BCL-2 antisense molecule-G3139; Results of phase I/IIA clinical trial

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Introduction: It has been well known that T14/18 translocation in follicular lymphoma up-regulates BCL-2, leading to continued expression of BCL-2 protein. Upregulation of BCL-2 leads to extended survival of the cells and increased chemoresistance. Clinical trials demonstrated correlation between BCL-2 expression and poor clinical prognosis in an intermediate and high grade lymphomas. G3139 is an all-phosphorothioate 18mer oligonucleotides targeted to the first six codons of the BCL-2 mRNA. It has been shown to specifically down regulate BCL-2 *in vitro* and to have dose dependent activity in mice models of human lymphoma as well as other xenograft models of solid tumours.

Methods: The Lymphoma Unit at the RMH performed the first Phase I trial in all grades NHL pts who relapsed following several previous conventional chemotherapy regimens and who expressed BCL-2. Replicating preclinical xenograft model, the patients received G3139 as a continuous, subcutaneous 14 day infusion. The doses were escalated according to EORTC scheme and safety as well as efficacy measured using standard evaluation criteria.

Results: Until early February 1997, 13 pts were entered in 6 dose escalation cohorts up to a dose of 147.2 mg/m^2/day. Based on excellent systemic tolerance the escalations were made in 100% increments. At the 6th dose level, reversible grade 3 thrombocytopenia was observed in 1 pt. Mild topical, infusion site irritation which was generally acceptable but two pts had more severe reversible reactions which were not dose dependent. Blood levels of two pts at 5th escalation level approximated concentration effective in *in vivo* models of lymphoma. In the first 9 pts, 4 pts demonstrated improvement in disease status as defined by clinical and.or laboratory parameters including decrease in BCL-2 protein. One of those 4 pts demonstrated minor tumour response. Another patient on the higher dose, who failed 4 prior therapies, with follicular grade II lymphoma, stage IVB, developed complete clinical and radiological response of 30+ week duration.

Conclusion: We conclude that antisense approach to BCL-2 constitutes a potentially important treatment modality in NHL, leading to responses in poor prognosis patients at doses causing low toxicity. The trial is continuing and the full update will be presented.

1181 ORAL

Management of stage I–II primary gastric non MALT-type lymphoma

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Purpose: Some therapeutic aspects of primary gastric non MALT-type lymphoma remain undefined. Impact on survival of gastrectomy as exclusive treatment, role of adjuvant chemotherapy (CHT) or radiotherapy (RT), use of RT in stage II and conservative treatment without gastrectomy were evaluated in a retrospective series

Patients and Methods: 136 pts with primary gastrointestinal NHL were reviewed. Pts with MALT lymphoma (n = 32), stage IV (n = 9) or extragastric sites (n = 9) were excluded. Study group consists of 86 pts: 43 with stage I, 23 with stage II_1 and 20 with stage II_2-disease. Median age was 62 ys (range 25–85). Seventy-three cases had intermediate- or high-grade lymphoma (IG-HG). Sixty-eight pts were submitted to surgical resection: as exclusive treatment (S) in 18 cases, followed by CHT (S-C) in 26, by RT (S-R) in 6 or by CHT and RT (S-C-R) in 18 cases. Eighteen pts did not undergo surgical resection, receiving only CHT followed or not by RT (conservative treatment).

Results: Sixty pts (70%) are alive (58 NED) at a median follow-up of 57 mo. Nineteen pts (22%) relapsed, 17 pts (20%) died of NHL and of 9 other causes (6 NED). There were no differences in relapse rate nor survival among pts with stage I treated with S alone, with S plus adjuvant CHT/RT or with conservative treatment. Partial or total gastrectomy showed similar relapse rate and survival among pts submitted either to S alone (p = 0.16) or to S followed by CHT and/or RT (p = 0.13). Addition of adjuvant CHT in pts with stage II and IG-HG significantly improved survival (56 mo, p = 0.01) in comparison to S alone (51 mo). Pts treated with S-C survived longer (62 mo) than pts submitted to S-R (9 mo, p = 0.009). Addition of RT to S did not improve local control nor survival (p = 0.16). S-C showed similar relapse rate and survival (62 mo) to S-C-R (73 mo, p = 0.24). Conservative treatment was associated to longer survival (67 mo) than S alone (51 mo) in pts with stage II-disease (p = 0.01). Conservative treatment showed a similar survival (66 mo) to S-C or S-C-R (57 mo, p = 0.23). Independent prognostic factors were age (p = 0.02), systemic symptoms (p = 0.009) and LDH level (p = 0.0006). Treatment modality showed prognostic value only among pts with stage II (p = 0.02).

Conclusions: Results with surgical or conservative treatments are excellent for pts with stage I. Extension of gastrectomy seems not to influence survival. CHT significantly improves survival in pts with stage II and IG-HG, and it should be preferred to RT as adjuvant therapy. Addition of RT to S or to S-C seems not to improved outcome. Since conservative treatment with CHT followed or not by RT obtains similar survival to S-C or S-C-R, surgical treatment should be indicated only for pts with high risk of bleeding or perforation with the aim to avoid the late-morbidity associated to gastrectomy.

1182 ORAL

Extended field (EF) and total central lymphatic (TCL) radiotherapy for early stages nodal centroblastic-centrocytic (CB-CC) lymphomas

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Purpose: A prospective multicenter trial was performed to evaluate survival and prognostic factors for patients with nodal cb-cc lymphoma in stages I–IIIA (≤5 involved regions) after EF and TCL radiotherapy.

Methods: 117 adults with clinical stage (CS) I–IIIA nodal cb-cc lymphoma were recruited. Patients with mediastinal or retroperitoneal stage I/II or stage IIIA lymphoma received TCL, the others EF radiotherapy. The whole abdomen was irradiated to 25.5 Gy (1.5 Gy/f), the mantel to 26 Gy (2 Gy/f); 5x2 Gy boost to macroscopic tumour. Age: 20–79 years; CS I/II/IIIA: 60/40/17; med. follow-up: 68 m.

Results: Overall survival at 8 years was 86%. The probabilities of nodal and disseminated extralymphatic relapses were 32% and 9% at 8 years. The dominant adverse prognostic factor for nodal in-field recurrences was a dose deviation below 80% of the prescribed dose (15 patients). After EF irradiation, patients in stage I had a significantly lower risk of nodal recurrences in adjuvant irradiated than in unirradiated lymph node regions. Acute toxicity was moderate.

Conclusion: This trial shows a steep dose-response relation between 26 and 36 Gy for cb/cc lymphoma. Adjuvant irradiation reduced the risk of nodal relapses per lymph node region. A randomised study of TCL vs. EF radiotherapy is in preparation by this group.

1183 ORAL

Quality control program of radiation therapy in EORTC H8 protocol: The French centers experience

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Rationale: The EORTC H8 protocol for early stage Hodgkin's disease include a precise definition of target volumes and dose. The aims of this study is to ensure that the radiation treatment effectively done is those required by the protocol.

Material and Methods: Each patient technical record was reviewed by all the radiation oncologists involved in the protocol of a given region (Paris, Lyon et Nancy), with a careful review of initial CT scans, simulation films, port films and radiation therapy data. For each target volumes, the quality of balistics (particularly the shape of the blocks) was judged adequate, doubtful or non adequate; and dose evaluated with DIF: DIF = (Dose received – dose provided by the protocol)/Dose received* 100.

Results: 161 patient records have been reviewed, 102 treated in involved fields (IF) and 59 with a subtotal nodal irradiation (STNI). We noticed