Proffered papers

Hematological and related malignancies

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HODGKIN'S DISEASE (HD), CLINICAL STAGES (CS) IA-IIIB WITHOUT BULKY TUMOR: INTERIM RESULTS OF THE GOELAMS RANDOMIZED H90-NM PROTOCOL

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From 2/90 to 6/93, 195 adult patients (pts) with HD, CS IA-IIIB without bulky tumor (nodes <10 cm; mediastinal tumor/thoracic width ratio <0.45; no simultaneous lumbo-aortic and pelvic involvement) were randomized to receive 3 monthly courses (only 1 in peripheral CS IA) of ABVD-MP (D1 and D15, mg/m^2: adriamycin 25, bleomycin (BLM) 10, vinblastin (VBL) 6, dacarbazin 375, methylprednisolone (MP) 120 = arm A, 101 pts) or EBVM-MP (D1 and D15, mg/m^2: epirubicin 30, BLM 10, VBL 6, methotrexate 30, MP 120 = arm E, 94 pts). CT-responding pts were given (sub)total nodal and splenic RT (involved fields 40 Gy, non-involved 30 Gy). Pts characteristics: M 110, F 85; age <= 40 148, >40 47; CS I 56, II 117, III 22; A 152, B 43; histology: LP 21, NS 128, MC 30, LD 1, UN 15. Complete remission rates after CT and RT were 81% (A 83 pts, E 74 pts) and 95% (A 96 pts, E 90 pts) (P = NS); 10 pts relapsed (A 1, E 9, $P < 0.05$) and 4 pts died (A 1, E 3).

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HIGH DOSE THERAPY AND AUTOLOGOUS BONE MARROW TRANSPLANTATION FOR RELAPSED OR REFRACTORY HODGKIN'S DISEASE: THE IMPACT OF TOTAL BODY IRRADIATION AND INVOLVED FIELD RADIATION THERAPY

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One hundred patients with relapsed/refractory Hodgkin's disease (HD) were treated with either high dose carmustine(BCNU)/etoposide(VP16)/cyclophosphamide(Cy) or fractionated total body irradiation (fTBI)/Vp16/Cy prior to autologous bone marrow transplantation (ABMT). In addition, 24 patients received involved field radiation therapy (RT) prior to (n = 18) or following (n = 6) ABMT. With a median follow-up of 30 months, 3-year actuarial freedom from relapse (FFR) and overall survival (OS) for the entire group are 65% and 63% respectively. By multivariate analyses, factors associated with recurrence were pleural disease (P = 0.009), pulmonary metastases (P = 0.004) and a poor response to cytoreductive therapy (P = 0.003). FFR and OS following BCNU/VP16/Cy (67% and 62%) or fTBI/VP16/Cy (60% and 60%) were similar (P = 0.51 and P = 0.49). A median RT dose of 30 Gy (range 14.4 Gy–45 Gy) was given to 67 sites in the 24 patients. Local failure occurred within 4 irradiated sites (6%) in two patients (8%). In patients with Ann Arbor stages I–III disease (n = 62), RT was associated with a trend toward improved FIR (92% -vs- 67%, P = 0.09) and OS (86% -vs- 59%, P = 0.13). Among patients not previously irradiated (n = 39), RT was associated with a significant improvement in FFR (85% -vs- 55%, P = 0.05) and OS (93% -vs- 54%, P = 0.03). Treatment related mortality (including 2nd malignancies) was similar with or without fTBI (15% -vs- 14%) or RT (17% -vs- 13%). In conjunction with high dose therapy and ABMT, RT is well tolerated, effectively controls local/regional disease, and may improve survival in selected patients.

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BREAST CANCER (BC) AFTER HODGKIN'S DISEASE (HD). ANALYSIS OF 35 CASES

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Introduction: The second cancers represents the most important problem among the survivors of HD. A possible link with chemotherapy (CT) and radiotherapy (RT) is suggested but genetic and immunologic factors may also be involved.

Material: In seven Cancer Centers, we found 35 women, previously treated for HD, who developed 37 BC. The median age at diagnosis of HD was 25 years, with 12 less than 20 years. HD stage was : I = 3, II = 21, III = 5, IV = 4, NS = 2. 33 women received supradiaphragmatic RT with doses varying from 35 to 45 Gy. 16 women received CT (mainly MOPP). The median interval between the diagnosis of HD and BC was 16 years. According to TNM, we found : 2 T0, 10 T1, 12 T2, 4 T3, 6 T4 and 3 Tx. 32 were ductal infiltrating carcinoma, 2 medullary, 2 *in situ* and one fibrosarcoma. Axillary involvement was present in 51% of cases. Mastectomy was performed in 23 cases, a radiosurgical conservative treatment in 12 and exclusive radiotherapy in 2. Fourteen women underwent chemotherapy.

Results: 7 women had local relapse of BC and 15 had metastases (40%). Three had contralateral metachronous BC. 17 women are in complete remission for both diseases; 15 died of BC. Three women died of intercurrent disease.

Conclusion: The women treated for HD, especially before 20 years, seem to have an increased risk of subsequent BC. According to other reports, we confirm that these BC are frequently aggressive, with rapid evolution and high risk of bilaterality. Consequently, a regular mammographic follow-up is necessary to detect these lesions earlier, to allow a better prognosis and a possible conservative treatment.

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IS RADIOTHERAPY CURATIVE FOR STAGE I–II LOW-GRADE FOLLICULAR LYMPHOMA?

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Outcome was reviewed for 180 stage I and II pts with follicular small cleaved cell (fsc; n = 103 [57%]) or follicular mixed small cleaved and large cell lymphoma (fmx; n = 77 [43%]), treated at Stanford 1961–1994. Pts received 35–50 Gy to one side of the diaphragm (involved or extended fields) or both sides of the diaphragm (total or subtotal lymphoid XRT). There were 74 (41%) stage I and 106 (59%) stage II pts. M/F ratio was 1.2. Median age was 53 yrs. Staging laparotomy (lap) was performed in 45 pts (25%) and 34 (19%) had extranodal lesions. Median follow-up (f/u) was 7.7 yrs; longest f/u was 31 yrs. Actuarial survivals at 5, 10, 15 and 20 yrs were 82%, 63%, 43% and 35% respectively. Actuarial freedom from relapse (FFR) was 55%, 44%, 43% and 35% respectively, at the same intervals. Median survival after relapse was 5 yrs. Only 5 of 47 pts at risk for more than 10 yrs after XRT have relapsed (latest relapse 21 yrs post XRT). Survival was worse for pts aged >40 yrs (P = 0.053) and worse still for pts aged >60 (P = 0.0001). FFR was also worse for pts aged >60 (P = 0.019). Multivariate analysis of prognostic factors indicated that youth and staging lap were most strongly associated with long survival and that treatment on both sides of the diaphragm and staging lap were most strongly associated with prolonged FFR. These data suggest that XRT alone is potentially curative for early-stage low-grade follicular lymphoma. Although >50% will relapse within 10 yrs, only 10% of pts at risk may relapse later. Early

relapses may be related to "under-staging" because lap-staged pts have superior FFR.

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MULTICENTRE RETROSPECTIVE REVIEW OF PRIMARY CUTANEOUS LYMPHOMA EXCLUDING MYCOSIS FUNGOIDES

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Seventy patients from five centres were identified as having primary cutaneous lymphoma (excluding mycosis fungoides and Sézary syndrome). All histology was reviewed and graded according to the Working Formulation (WF) or updated Kiel classification. Full staging was performed to exclude extracutaneous disease at presentation. The median age was 58 (91–25); male:female ratio 1.7:1; 46 patients presented with solitary lesions (9 with satellite lesions), in 10 patients the distribution was generalised. There were 11 low grade lymphomas (WF A-C)—9 B-cell, 2 T-cell and 59 high grade tumours (WF E-H, LCA,)—33 B-cell, 10 T-cell, 16 immunohistochemistries were non-evaluable. The complete response (CR) rate to first treatment was 80% (56/70) and the CR rate for solitary lesions treated with radiotherapy was 92% (23/25). The lymphoma specific progression free survival was 75% at 1 year, 51% at 5 years with a median of 107 months. Median follow up was 47 months. Twenty-five patients (36%) had at least one cutaneous relapse and 8 (11%) developed an extracutaneous relapse. The risk factors for relapse were >5 lesions ($P < 0.025$) and in solitary lesions the presence of satellites ($P < 0.005$). Overall survival at 5 years was 79% and lymphoma specific survival was 84%: 3 patients died of unrelated causes in remission, 4 died with skin lymphoma but no extracutaneous disease, 6 died from disseminated lymphoma. All patients dying from lymphoma had high grade histology. Prognostic factors for poor disease specific survival were age > 60 ($P < 0.005$) and >5 lesions ($P < 0.005$). Conversely patients with solitary lesions had a better survival ($P < 0.005$). In conclusion primary cutaneous lymphoma has a high survival rate despite frequent cutaneous relapses.

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TOTAL THERAPY OF ACUTE MYELOID LEUKAEMIA

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Our *total therapy* programme for AML comprises chemotherapy followed by BMT in CR1. From 4/90 to 12/94, 54 pts (13–53 y, med 33.5) received BF12 induction: high-dose ARA-C and VP-16 with idarubicin or mitoxantrone followed by two consolidation cycles. 42 pts attained CR (78%). 32 underwent BMT in CR1; one is awaiting BMT. Of the nine not transplanted in CR1 (early relapse, n = 7; refusal, n = 1; death in CR, n = 1), one was transplanted in rel1 and five in CR2.

Subgroup	No.	Cont. CR	Relapse	Toxic deaths	Total deaths	Total alive
Whole group	54				25	29 (54%)
Overall CR	42	23	12	7	13	29 (69%)
ABMT in CR1	19	14	3	2	5	14 (71%)
Allo in CR1	12	7	1	4	5	7 (58%)
Twin in CR1	1	1	-	-	-	1
No BMT in CR1	10	1	8	1	3	7 (70%)

With 54% survival at 3–59 months (median 31) after diagnosis, we believe that this *total therapy* programme represents state-of-the-art management of AML.

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ALTERNATING VCMP/VBAP AT STANDARD DOSES (SD) VS. VCMP/VBAP AT INTERMEDIATE DOSES (ID) AS INITIAL TREATMENT OF MULTIPLE MYELOMA (MM)

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In a previous PETHEMA study we have shown that VCMP/VBAP increases response rate in MM when compared with melphalan/prednisone. The aim of the present study was to ascertain whether treatment with VCMP/VBAP (ID) with a moderate increase in the cyclophosphamide (C) and adriamycin (A) doses could be superior to VCMP/VBAP at SD.

From Jan 1, 1990 through May 31, 1994, 449 pts with symptomatic MM entered the study. All patients were randomized to receive: (A) alternating courses of VCMP (vincristine 1 mg iv on day 1, cyclophosphamide 500 mg/m^2 iv on day 1, melphalan 9 mg/m^2 p.o. on days 1–4 and prednisone 60 mg/m^2 on days 1–4) and VBAP (vincristine 1 mg iv; BCNU and adriamycin iv, 30 mg/m^2 each on day 1; and prednisone 60 mg/m^2 on days 1–4, or (B) the same VCMP/VBAP increasing the cyclo from 500 to 1200 mg/m^2 and adria from 30 to 50 mg/m^2. The objective response rate among the already evaluable pts for response was 40.2% with SD vs 50.5% with ID ($P = 0.068$) with no impact on survival (31 vs 30 mos).

In summary, these results show a trend towards a higher response rate to VCMP/VBAP at higher doses of cyclo and adria, with no significant impact on survival.

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EFFECT OF CLODRONATE ON PROGRESSION OF SKELETAL DISEASE IN MULTIPLE MYELOMATOSIS

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We have examined the effect of clodronate on skeletal morbidity in myeloma in a double-blind placebo controlled trial. 615 patients were randomised at diagnosis to receive either clodronate 1600 mg daily by mouth (n = 304) or an identical placebo (n = 305) in addition to chemotherapy.

There was no difference in the initial symptomatic response between the clodronate and placebo-treated patients. In contrast, at relapse, the proportion of patients with poor performance status was significantly lower in those receiving clodronate (RR 0.52, 95CI 0.32–0.83). Fewer patients experienced a marked increase in back pain (RR 0.48, 95CI 0.13–0.89) and a similar trend was observed for rib pain (RR 0.34, 95CI 0.10–1.21). Fewer patients experienced new vertebral fractures after the first year in the clodronate wing (RR 0.72, 95CI 0.51–1.01) with fracture rates of 33 and 54 new fractures/100 patient years respectively ($P < 0.003$).

We conclude that long-term oral clodronate modifies the progression of skeletal disease and provides a useful adjunct to clinical management.

776 POSTER

AIDS-RELATED MALIGNANCIES: ANALYSIS OF 168 CASES REGISTERED IN ALSACE

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In 1989, the regional reference center for HIV infection in Strasbourg decided to set up a prospective study of the incidence of all malignancies occurring in HIV-infected individuals followed up at the three major hospitals of the Alsace region.

As of March 15, 1995, 168 HIV-associated malignancies have been recorded in 165 patients through anonymous notification to the reference center.

Sex-ratio is 9.3 (149 men, 16 women) and mean age 35.8 (22–61). Kaposi Sarcoma is the most frequent neoplasia (100 cases, 59%) occurring mainly in male (96 cases) among which 83 (86%) are homo- or bisexuals. 65% of Kaposi's sarcoma are the first AIDS-defining event. Non-Hodgkin lymphomas (39) are essentially of high grade of malignancy and of B type and are the first AIDS-defining event in 19 cases (49%).