was 225/mmc (range 32-1008) and 27 pts had a detectable HIV viral load (median 3600 copies/mmc (range 60- 455000). Stage III and IV disease was present in 33/46 (72%) pts. Histologic subtypes were: MC 43%, NS 24%, LD 6%, not determined 26%. As far as toxicity, no toxic death was observed, while an absolute neutrophil count <500 was observed in 37 out of 46 pts (80%). Grade 4 anemia was observed in 20/46 pts (43%) and severe thrombocitopenia in 8/46 (17%) pts. Thirteen pts (28%) had febrile neutropenia with 3 documented bacterial sepsis. A grade 2-3 peripheral neuropathy was observed in 15/46 pts (33%). CR was obtained in 37/45 pts (82%) and PR in 4/45 pts (9%). Seven CR pts relapsed (19%). The actuarial overall survival and disease free survival at 2 years are 57% and 66%, respectively. Our preliminary data demonstrated that the abbreviated CT regimen, Stanford V, in combination with HAART is feasible and active in pts with HD-HIV. Supported by AIRC and ISS grants.

320 POSTER

Outcome of very late relapse of Hodgkin's disease (HD) at the National Cancer Institute of Milan

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Purpose: HD is a highly curable neoplasm,however very late relapse, occurring more than 10 years after achieving CR with first line therapy,is rare but not uncommon.We report the outcome of 13 pts relapsing more than 10 years after CR.

Methods: Among 523 pts enrolled at our institution in prospective studies and in CR after first line treatment 13 pts(2.5%)relapsed after a median of 179 months (range 123-216).Main pt characteristics at relapse were as follows:median age 40 years(range 29-66);males/females 9/4;stage I+II/III+IV 6/7;B symptoms 2.Treatment at relapse was:RT alone in 1,ABVD in 2,MOPP/ABVD in 8,MOPP in 1 and Vinorelbin+Prednisone in 1 case.Consolidation RT on nodal involved and not previously irradiated sites was delivered at the end of chemotherapy(CT) in 6 pts.

Results: Eleven pts (85%) achieved a 2nd CR,while 2 pts failed.Eight pts (64%) are alive and disease-free after a median of 84 months (range 26-180) from start of salvage CT,one pt relapsed subsequently and was salvaged by high-dose CT+PBSC reinfusion,for a total of 9 pts (69%) alive at 61 months (range 26-180).Two pts died in CR from HD:one for heart failure and one for metastatic gastric cancer.One pt,aged 66 years and in continuous CR,developed a myelodisplasia 26 months after the end of second line therapy.

Conclusion: This study confirms that the percentage of pts relapsing more than 10 years from the end of first line treatment is very low (2.5%).Taking into account the long event-free survival experienced by 61% of our pts,we suggest that conventional-dose salvage CT should be the treatment of choice in this favorable subset of HD pts with very late relapse.

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Analysis of second cancers following Hodgkin's disease treatment

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Introduction: Cardiovascular complications and secondary cancers after Hodgkin's disease (HD), concern more than any other side-effect because of their direct impact on the survival. Both are linked to radiotherapy and limiting its role in the cure of HD is under investigation. But however the role of other factors has to be underlined such as smoking, alcohol, thyroid impairment, female hormonal status and occupational exposition or immunosuppression.

Method: We carried out a retrospective study of all second cancers in a cohort of HD treated in our institution and analysed factors favouring second cancers, assuming that in our centre we never performed staging laparotomy, but combined modality treatment.

Results: Among 920 patients treated since 1960 and with a median follow up of 11.5 years (min 2- max 38) 76 cases of second cancers were detected.

Most of them occurred in irradiated areas confirming the role of radiotherapy. But some were far from radiotherapy fields in urinary tract (kidney, bladder, ureter, gall bladder, colon and lymphomas) suggesting the role of either chemotherapy or some other factors. The median time to second cancer is 141 months and the survival since its occurrence shows a 5-year overall survival of 25% indicating that this complication remains highly life threatening and deserves prevention by a more adapted treatment for initial HD.

Cancer type	Number (%)
Non Hodgkin's lymphomas	13 (17.1)
Lung or throat cancers	10 (13.2)
Renal or urothelial carcinomas	6 (8)
Digestive carcinomas	7 (9.2)
Thyroid carcinoma	4 (5.2)
Breast cancer (among 338 females)	9 (12)
Skin carcinoma & melanoma	4 (5.2)
Sarcomas	4 (5.2)
Acute leukaemia	12 (15.8)
Undetermined origin	4 (5.2)
Miscellaneous (brain, ovary)	3 (4)

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Hodgkin's disease among patients older than 60

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Introduction: Old patients (pts) with Hodgkin';s disease (HD) are usually excluded from trials and information for such pts are rare. Many publications stressed that HD of the elderly may be a different entity, which explains the poorer prognosis. Old patients have usually a lot of comorbidity, limiting curative chemotherapy.

Method: We analysed clinical characteristics of old pts with two limits to define the elderly: over 60 and over 70 years dispatched in three cohorts of <60, 60 to 70 and >70. Initial characteristics concerning sex, stage, mediastinum, pathology, biological data, treatment and results were reviewed.

Results: Among 912 pts with more than 3 years follow up, 128 were over 60, 70 between 60-70 and 58 over 70. Sex ratio was similar to that of the young (ns). Histology type 3 was significantly more frequent (50% vs 30%, P=0.0001) and mediastinum involvement was less frequent with a linear association with age (p value<0.000001). Bulky disease, percentage of limited or extended stages, systemic symptoms, E-extension or compressive behaviour were in the same percentage than among young pts (ns in all comparisons). Treatment strategy was similar to that of the young HD with combined modality treatment for stages I & II and chemotherapy alone for extended stages, 10% of patients had radiotherapy alone. Analysis of response failed to show a difference between the young and the old in term of complete remission. For relapse, there is no difference between group 60-70 year and the young (19.4% vs 18%), but there are more relapses for the very old (38% vs 19.4%, p=0.0007) when compared to the younger groups. 5 year overall survival is not very good (40%, 60% and 90% according to age) the specific survival including only HD and treatment toxicity related deaths displays a better survival (63% vs 75% vs 89% respectively).

Conclusion: According to this study there is not major difference between young and old HD excepting histology and medistinum involvement. The primary treatment response is roughly the same. However the higher rate of relapse and a worse cause specific survival may reflect the fact that these patients has not the necessary amount of chemotherapy and justify a specific and adapted regimen for these pts.

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Prospective randomized trial in the treatment of early stage hodgkin's disease (ESHD) using involved field radiation therapy (IFRT) vs. subtotal nodal irradiation (STNI) after a short chemotherapy (CT) course

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Purpose: The aims of this prospective, monoinstitutional trial are to evaluate: a)whether or not short course CT (ABVD 4 cycles) plus RT improves the freedom from progression (FFP) and the overall survival (OS) rates in

ESHD patients (pts); b)the optimum extension of RT fields (IF vs STN); c)treatment releated toxicity.

Methods: From February 1990 to July 1996, 140 consecutive pts with no laparotomy proven HD, staged I bulky and/or B, IIA, IIA bulky and IIEA, were randomized to receive either 4 cycles ABVD plus IFRT or 4 cycles ABVD plus STNI. ABVD dose intensity was 0,84. RT doses were 30 Gy to uninvolved sites, 36 Gy to involved sites and 40 Gy respectively to partial responders sites.

Results: After a median follow-up of 87 months, 136 pts (median aged 29; range 17-64) are evaluable. Treatment outcomes are as follow: ABVD+STNI (66 pts): complete remission (CR)=100%; FFP=97%; OS=93%; ABVD+IFRT (70pts): CR=97%; FFP=94%; OS=94%. 30% pts achieved CR after the third ABVD cycle; 88% after the fourth. 14/15 partial responders achieved CR with RT. One pt developed acute leukemia in the STNI arm. Acute and late toxicities were mild.

Conclusion: 4 ABVD courses plus IFRT are an effective treatment in ESHD with mild toxicity.

Supported in part by Associazione Italiana Ricerca sul Cancro - Milano

Adult leukemia

324 POSTER

Molecular biology of acute promyelocytic leukemia (APL) in peruvian patients: PML/RAR alfa isoforms distribution in latino patients

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Background: APL is a distinctive form of AML genetically defined for presence of PML/RAR alpha fusion gene in most of the cases, with a distribution of 54-57% of long isoform (bcr1), 8-10% of variable(bcr2) and 37-40% of short isoform(bcr3)(bcr1/bcr3 ratio 1.4:1) An unexplained higher than expected frequency of APL (>20% of all AML) has been previously reported in "latino" populations as ours; however no differences in molecular characteristics have been determined for these populations.

Methods: We evaluated 24 peruvian pts. diagnosed of APL between March 1998 to December 2000 to determine molecular and clinical characteristics in this "latino" population. All pts. had morphological, cytochemical and conventional cytogenetics studies and RT-PCR for RNA analysis for PML/RAR alpha isoforms.

Results: 22/24 pts. with evaluable molecular results are included in this report. Ethnicity of all pts. were mestizo ("latinos"). Median age was 18.6 years old, F/M ratio: 1.2/1.0; FAB morphology was hypergranular in 17/22 (77.2%) and variant in 5/22 (22.7%). Cytogenetics showed t(15,17) in 65% of pts., however all pts. had confirmed molecular diagnosis of APL by PCR. Distribution of PML/RAR alfa isoforms was:long (bcr1) in 16/22 (72.7%), variable (bcr2) in 1/22 (4.5%) and short (bcr3) in 5/22(22.7%). All pts. were treated with IV Liposomal Atra followed by chemotherapy. Characteristics of pts. according to molecular isoforms are: a)Long Isoform (n:17): median age 17, with 31% of high risk pts.(Sanz Index),25% of ATRA syndrome and 86.7%of pts. achieving complete response(CR).

b) Short Isoform(n:5):median age 30, with 20% of HR pts.,40% of ATRA syndrome and only 50% of CR pts.

c) Variable Isoform: only one pediatric high risk pt (7 years old),who failed to achieve CR.

Our data shows a higher than expected frequency of long isoform in latino or mestizo population in Peru with a higher bcr1:bcr3 ratio(3.1:1) compared with prior reported series. We also observed a tendency of older age, higher ATRA syndrome frequency and lower ATRA sensibility associated with short isoform.

In conclusion our serie shows a distinctive molecular expression of APL-specific PML/RAR alpha gene in latino (mestizo) population in Peru, different from reported in other ethnicities. Further molecular analysis of APL in "latino" populations will allow us to understand the biological and clinical significance of these findings.

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Inhibition of ribonucleotide reductase by trimidox potentiates the cytotoxic and apoptotic effects of Ara-C in HL-60 human promyelocytic leukaemia cells

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The enzyme ribonucleotide reductase (RR) catalyzes the rate limiting step of the de novo synthesis of deoxynucleosidtriphosphates (dNTPs). Its significantly increased activity in malignant tumor cells makes this enzyme an excellent target for cancer chemotherapy. Trimidox (3,4,5 trihydroxybenzamidoxime) was proven a potent inhibitor of RR causing a significant depletion of dCTP pools in HL-60 human promyelocytic leukaemia cells. In the present investigation we analyzed the effects of a combination treatment regimen using trimidox and Ara-C, a well established chemotherapeutical agent for the treatment of leukaemia. Deoxycitidinekinase, the enzyme which activates Ara-C by phosphorilation underlies a negative feedback mechanism by dCTP, therefore a decrease in dCTP levels results in an increase of Ara-C metabolism and the incorporation of Ara-C into DNA.

We investigated the effects of a treatment with trimidox on the incorporation of radiolabelled Ara-C into DNA and found that trimidox synergistically enhanced the incorporation of Ara-C. Preincubation of HL-60 cells with 75 and 100 μM trimidox caused an increase in Ara-CTP pools by 90 and 150% compared to control values, respectively, which resulted in a 1.51 fold (with 75μM trimidox) and 1.89-fold (with 100μM trimidox) increase in Ara-C incorporation into DNA. Synergistic cytotoxic effects of combination treatment using Ara-C and trimidox were also confirmed by colony formation and growth inhibition assays. In growth inhibition assay, a synergistic combination index of >1 was yielded by treating the cells with 15 μM trimidox combined with 5 and 10 nM Ara-C. In soft agar colony formation assay the combination of 0.5 and 0.75 μM trimidox with 0.5-3 nM Ara-C showed significant synergism. We also found that the combination of 5 and 10 nM Ara-C with 10 and 15 μM trimidox resulted in the potentiation of the apoptotic effects of Ara-C. We conclude that trimidox is able to synergistically enhance the cytotoxic and apoptotic effects of Ara-C and therefore might be considered a valuable alternative for the combination chemotherapy of leukaemia.

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Salvage therapy combining high-dose cytarabine with amsacrine in refractory acute myeloid leukemia (AML): analysis of prognostic factors

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Refractory AML have a very poor prognosis. High-dose cytarabine (HD-AraC) has been proposed as salvage therapy in combination with amsacrine. The aim of this study was to assess toxicity and efficacy of this combination. Prognostic factors were also assess in order to determine patients susceptible to benefit of such a therapy. 91 patients referred to our hospital have been treated by HD-AraC (3 g/m2/12 hours for 4 days) combined with amsacrine (90 mg/m2/d for 3 days). 69 and 22 patients failed to one course of chemotherapy according respectively to the LYLAM85 or the LAM90 protocol. 45/91 patients (50%, 95% CI: 39-60%) achieved CR. 35 patients were refractory to the salvage therapy and 11 died from toxicity. Median DFS was 12 months. 26 patients received consolidation therapy. 19 patients with an HLA-identical sibling donor underwent allogeneic transplant. 27/45 patients (60%) who achieved CR have relapsed. Median OS was 10 months. There was 12 long survivors (13%). Karyotype was the main prognostic factor for CR achievement ($p = 0.001$), DFS ($p = 0.01$) and OS ($p = 0.0009$). In univariate analysis, CR achievement was also related to WHO performance status < 2 ($p = 0.007$), LDH level ($p = 0.02$), CD34 expression ($p = 0.03$) at diagnosis; platelet > 80 G/l ($p = 0.0001$), and the absence of circulating blasts ($p = 0.001$) and biological abnormalities ($p = 0.009$) before salvage therapy. DFS was negatively influenced by weight loss ($p = 0.03$), and WBC count > 10 G/l ($p = 0.03$) at diagnosis; and biological abnormalities before the salvage regimen ($p = 0.007$). Age ($p = 0.002$), toxic exposure ($p = 0.01$), CD34 expression ($p = 0.02$), weight loss ($p = 0.006$), and performance status > 2 ($p = 0.01$) at diagnosis; platelet < 80 G/l ($p = 0.02$), and biological abnormalities ($p = 0.0003$) were associated with shorter OS. In multivariate analysis, CD34 expression ($p = 0.001$), LDH level ($p = 0.02$), biological abnormalities ($p = 0.007$), and circulating blasts