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

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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