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MAINTENANCE LOW-DOSE (LD) ORAL IDARUBICIN (oIDA) IN ELDERLY PATIENTS (pts) WITH ACUTE MYELOGENEOUS LEUKEMIA (AML)

M. Musso*, F. Porretto*, A. Crescimanno*, V. Polizzi*, F. Bondi*, A. Patti**, R. Perricone*, A. Cajozzo*.
* *Dept. of Haematology/BMT Unit, University of Palermo, Italy.* ** *Pharmacia & Upjohn.*

IDA by i.v. route, especially in combination with cytosine arabinoside (Ara-C), proved quite effective for intensive chemotherapy of AML However, persisting controversies on aggressive/intensive *versus* "attenuated" regimens for elderly AML pts emphasize the interest of oIDA in this latter setting (cf M.R. Howard *et al.*, and M.J. Keating, Clin. Drug Invest. 1995; 9, Suppl. 2: 16-38).

A 69% complete response (CR) rate was recently reported (F. Leoni *et al.*, Br. J. Haematol. 1995; 90: 169-174) among 25 elderly AML pts (> 60 yrs old) with an "attenuated" dose of IDA, i.e. 8 mg/m^2 i.v. d. 1, 3, and 5, plus Ara-C 200 mg/m^2 by continuous i.v. infusion (CIV) d. 1-7, and etoposide (VP-16) 60 mg/m^2 i.v. d. 1-5. The areas under the curve (AUC) of plasma concentrations/time of both unchanged IDA and of its uniquely active 13-OH metabolite, Idarubicinol (IDAol), in a group of 8 elderly recipients of IDA 8 mg/m^2 were closely comparable to those recorded in 9 younger AML pts treated with standard-dose IDA (12 mg/m^2). Importantly, due to first-pass liver metabolism, the yield of IDAol with oIDA is about twofold that achieved with i.v. administration.

We (Musso *et al.*, Eur. J. Cancer 1994; 30, Suppl. 1: S37) reported 4 CR and 4 CR out of 11 evaluable elderly (age range 67 to 81 years) AML pts with an "attenuated" regimen of oIDA 20 mg/m^2 daily d. 1-3 q 3-4 wks.

Subsequently, based on the assumption that sustained, chronic exposure to LD-oIDA could control minimal residual disease (MRD), possibly *via* cell-differentiating and/or apoptogenic stimuli, we enrolled ten previous responders to standard induction chemotherapy for AML (IDA 8 mg/m^2 i.v. d. 1-3, VP-16 100 mg/m^2 d. 1-3 i.v., and Ara-C 100 mg/m^2 d. 1-5 CIV) to receive maintenance oIDA 5 mg daily d. 1-14 at 2-wk intervals for at least 6 months.

Long-term LD-oIDA was well tolerated. Dose-limiting myelosuppression was modest, with leukocyte (WBC) and platelet (PLT) nadirs ≥ 500 and 50,000× 10^9/l, respectively, and without any infectious complications. Nonhematological toxicities were also acceptable: nausea/vomiting easily managed, no recorded diarrhea or mucositis. The convenience or oral administration contributed to excellent compliance. Plasma IDA and IDAol were monitored during the treatment. In conclusion, long-term LD-oIDA would appear valuable as a maintenance regimen.

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IDARUBICIN vs MITOXANTRONE IN A CONTINOUS-INFUSION CYCLOPHOSPHAMIDE PLUS DEXAMETHASONE REGIMEN FOR ADVANCED REFRACTORY MYELOMA

C.Nozzoli, S.Ciolli, F.Leoni, C.Marrani, A.Pascarella, F.Salti, R.Caporale, P.Rossi Ferrini. Department of Hematology, 50134 Florence, Italy

In the aim of increase the response rate, we replaced VM-26 with idarubicin (IDA) or mitoxantrone (MITOX) in a salvage regimen consisting of cyclophosphamide (CY) by continous iv infusion plus dexamethasone (DEX), previously reported by us as active in advanced refractory myeloma. 23 pts were randomly assigned to receive monthly courses of 6 mg/mq/d iv IDA (no pts 12) or MITOX (no pts 11) on days 1-2 , CY 200 mg/mq and DEX 40 mg iv from day 1 to 7. Eight were primary refractory to MP therapy, 15 were relapsed and refractory to salvage regimens (VAD, VMCP). Median age was 60 yrs (48-70), months from diagnosis 33 (3-140). Four pts were stage II, 19 stage III, 4 had B condition (D & S). 14 were IgG, 7 IgA, 2 BJ. RESULTS: a total of 79 courses were delivered. The response was evaluated after 2-3 courses. Overall, 13 pts (57%) were responders, achieving > 30% reduction of the M component; 7 (30%) were non responders and 3 (13%) died early (2 pulmonary edema,1 cerebral hemorrhage). All pts experienced transient leukopenia (median 0.9 WBC), promptly recovered after G-CSF. None had to delay the next course due to leukopenia. Extrahematological toxicity consisted mainly of infections, with gram-positive pneumonia in 4 pts. One pt, although responder, was taken off the study after 1 cycle for severe arythmia. In conclusion, preliminary results suggest that this regimen is effective and feasible with acceptable toxicity. The study is ongoing, a longer follow-up is required to asses the impact on survival.

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PROGNOSTIC FACTORS IN ACUTE LEUKEMIAS

E. Ozyilkan, S. Ariogul, E. Karaagaoglu
Ondokuz Mayis University Faculty of Medicine, Samsun and Hacettepe University Faculty of Medicine, Ankara, Turkey

Pretreatment prognostic factors were evaluated in 173 patients with acute myeloid leukemia (AML) and 78 patients with acute lymphoblastic leukemia (ALL) followed between 1980 and 1990. The effects of factors to survival were analysed by log-rank test. In AML cases, patients between 17-31 years age, who were symptomatic for less than 2 months, with blast cells less than 60% in peripheral blood smear, without infection, followed between 1985-1990 lived longer ($p<0.05$). In ALL cases, patients without infection and hemoglobin values more than 7gr/dl lived longer ($p<0.05$). In both leukemias patients who achieved complete remission (CR) with treatment lived longer than patients without CR ($p<0.01$).
Factors that may be important in CR were evaluated by multivariate regression analyses. In AML cases, age, follow up period, white blood cell count (WBC), and symptoms duration were found important in achieving CR ($p=0.006$, $p=0.049$, $p=0.171$, and $p=0.212$, respectively). In ALL cases, age, follow up period, Blast percent in peripheral blood smear, WBC, and platelet count were found important for CR ($p=0.021$, $p=0.038$, $p=0.072$, $p=0.150$ and $p=0.192$, respectively). In conclusion, we decided that some pretreatment factors were important both in survival and CR in acute leukemia patients.

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IMMUNE PROFILE IN CHRONIC LYMPHOCYTIC LEUKEMIA

S Paydas, B Şahin, S Çetiner
Çukurova University, Faculty of medicine, Dept of Oncology ADANA/TURKEY

Immune profile in 29 cases with chronic lymphocytic leukemia (CLL) and 1 case with Richter's Syndrome was evaluated and compared with other prognostic parameters including disease stage, organomegaly, hematocrit, WBC count, platelet, bone marrow involvement pattern, serum albumin and globulin profile and response to therapy. Monoclonal antibody panel included CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11b, CD13, CD14, CD19, CD20, CD22, CD23 and CD33. Surface antigenic expressions were as follows: CD2 ; in 5 of 16 cases (31%), CD3; in 2 of 23 cases (9%), CD4; in 2 of 16 cases (13%), CD5; in 24 of 27 cases (89%), CD7; in 11 of 26 cases (42%), CD8; in 1 of 17 cases (6%), CD10; in 1 of 24 cases (4%-who was the case of Richter's Syndrome), CD11b; in none of the 11 cases, CD13; in 10 of 19 cases (53%), CD14; in none of 12 cases, CD19; in 27 of 29 cases (93%), CD20; in 5 of 15 cases (33%), CD22; in 5 of 8 cases (63%) and CD33; in 1 of 15 cases (6%). Between surface antigenic expressions, CD2 and CD7 expressions were associated with higher frequency of CD5 negativity as compared cases not expressing these antigens. When compared antigenic expressions and with other parameters, it has been found that: CD2 expression was associated with lower WBC count, lower incidence of thrombocytopenia and splenomegaly and higher globulin value and higher incidence of thrombocytopenia and advanced stage disease. CD4 expression was associated with poorer response to therapy, CD7 was associated with higher incidence of hepatomegaly, CD8 was associated with lower Hct value. CD13 expression was associated with higher WBC count and more advanced stage disease. CD19 was associated with low risk of hepatomegaly, CD20 was associated with low risk of lymphadenopathy. CD22 was associated with lower incidence of hepatomegaly and well response to therapy.

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MODIFIED C/MOPP-A/EBV IN HD PATIENTS

Płużańska A., Chmielowska E., Stefaniak P., Zambrano O.
Chemotherapy Dept., Medical University of Łódź, Poland

Eighty eight consecutive pts with advanced HD were treated in 1990-1994 according to a seven drug regimen (modified MOPP-AEBV, 2nd inj. on 15th instead of 8th day). Clinical data: M-42, F-46, age 17-60 (av. 38). Clinical stage II (with worse prognostic factors)-42 (52,5%) pts, III - 26 (32,5%) and IV - 12 (15%), B symptoms - 54 (67,2%) pts. Results were evaluated in 84 pts according to commonly accepted criteria.
After 3-6 cycles of CHT we observed CR in 63 (78,8%) pts, PR in 10 (12,5%) pts, NR in 7 (8,8%) pts. CR occured in 38 (94%) pts with stage II of HD and 25 (65,8%) pts with stage III-IV of the disease. Patients without CR after 3-4 cycles were treated according to another schemes.
Hematologic side effects: anemia, leukopenia and trombopenia III-IV were observed respectively after 0, 9 and 1 in 422 cycles of CHT.
53 pts among 63 from the CR group are still in CR. DFS in this group is 6-69 months (av. 32 mths). Overall survival for all pts is 489 months (av. 30 mths).

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ORAL IDARUBICIN (oIDA) IN ELDERLY PATIENTS (pts) WITH ACUTE MYELOGENOUS LEUKEMIA (AML): AN OPPORTUNITY ?

F.C.A. Visentin, F. Ganzina, J. Smeets, M. Rizzi — Pharmacia & Upjohn

IDA, besides its unique peculiarity of oral as well as i.v. administration, exhibits intriguing potentials for (partially) reverting Pgp/*mdr*-1-related MultiDrug Resistance (MDR), especially relevant in hematological malignancies, as well as for killing noncycling/resting bone marrow precursors, possibly *via* stimulation of apoptosis. Compared to i.v. IDA, oIDA yields a twofold amount of its uniquely effective OH-13 metabolite, IDAol, equally active and myelotoxic as the parent IDA. Thus, although oIDA cannot be meaningfully introduced in *intensive* chemotherapy (CT), it was proposed for elderly pts with AML. Conventionally, pts over 60 are considered as elderly, and *overall* they had lower CR and higher toxic death rates compared to younger adults, even if recent reports emphasize the need for risk-adjusted treatment, tailored to the biological rather than chronological age of the individual pts.
Based on data from published trials in elderly AML patients,

Author/Year	Patient Population	Regimen (mg/m^2)	CR CR/pts	CR %	CR, median duration, wks	% Deaths on induction	MST, wks
Harousseau, 1989	> 65 yrs, untreated	oIDA 30 × 3 d	8/20	40	21+	25	20
Harousseau, 1991	> 65 yrs, untreated	oIDA 20 × 3 d LD Ara-C s.c.	13/32	41	25	19	23
Ruutu, 1994	> 65 yrs, untreated	ETI* *vs* TAD*	15/25 6/26	60 23	30 12	4 23	40 15
Pagano, 1991	> 60 yrs, untreated/ pretreated	oIDA 25 × 3 d Ara-C s.c.	8/17	47	22	23	49 (in responders)
Heig, 1990	> 65 yrs, untreated/ pretreated	oIDA 30 × 3 d LD Ara-C s.c.	14/26	53	20	19	Not available
TOTAL 58/120 48% CR							

* ETI: VP-16 *p.o.* 160 mg/m^2 daily × 5 d; 6-TG *p.o.* 200 mg/m^2 daily × 5 d; oIDA 15 mg/m^2 daily × 3 d.
TAD: 6-TG *p.o.* 200 mg/m^2 daily × 5 d; Ara-C i.v. 200 mg/m^2 daily × 5 d; Daunorubicin i.v. 60 mg/m^2 × 1 d.

oIDA, both as a single-agent and as a component of fully or partially oral combinations with cytosine arabinoside (Ara-C), etoposide (VP-16), or 6-thioguanine (6-TG), proved effective. However it should not be understood as *attenuated* CT, on account of significant myelotoxicity, anyway precluding outpatient treatment (especially at doses > 15 mg/m^2 daily × 3). Indeed, cumulated evidence appears to suggest use of hematopoietic support. Other, strictly investigational approaches are: 1) Induction with chronic low-dose oIDA in poor-risk pts, unfit for aggressive/intensive CT, and 2) use of an oral regimen as postremission treatment following a standard "intensive" i.v. CT..