Diagnosis, Treatment and Prognostic Factors in Leukaemias and Lymphomas

180

IN-HOME SUPPORTIVE THERAPY AND LD-ARA-C FOR HIGH RISK ACUTE LEUKEMIC ELDERLY PATIENTS

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New opportunities for nursing and confort-care should be contrived for leukemic elderly pts with poor general conditions, severe comorbidity or resistant disease. We have set up an unterdisciplinary teamwork endovouring to provide for uninterrupted and integrated medical care for such pts by a complete IN-HOME SERVICE supplying antileukemic therapy, transfusional supports in ipo/aplasia, palliative care.

Aims: 1) Good control of disease progression by chemotherapic regimens devoid of any relevant extrahematological toxicity, 2) delivering adequate supportive therapy (transfusional, antimicrobial, nutritional); 3) a dignified quality of life; 4) palliative care for terminal illness.

Inclusion criteria: 1) resistant disease 2) inegibility for conventional protocols due to severe comorbidity (cardiac, hepatic), refusal of hospital setting, refusal of consent for aggressive treatment.

Patients: 11 acute leukemic elderly pts (7 'de novo' AML:FAB M1=3, M2=3, M4=1, 2 'secondary' AML: FAB M1=2; 2 CML myeloid blast crisis; M/F=7/4; median age=72, range 66-83; Kamofsky PS median 50%, range 30-70%) throughout the phase of active treatment, post treatment monitoring and palliative care.

Methods: 1) Continous home health care 2) treatment by LD-AraC 12 mg/m^2 twice daily s.c. or by c.i. for 7-21 days

Results: Continous home-care for a median time of 156 days (range,38-572) and a median number of 4 courses of LD-AC (range,4-14) delivered; 2)Three Complete Remissions (4, 8 and 16 months) in AML FAB M2 pts, the CML-BC pts enjoyed a good PS for 3 and 5 months 3) low incidence of WHO 2-3 infections 4) in-home safe handling of Hickman lines and adequate transfusional and antimicrobial supportive therapy 5) terminal ill patient cared for by family with more intimacy.

Our home-care executive planning is detailed and the patients outcomes are discussed.

181

DOSE-DEPENDENT DISSOCIATION OF EFFECTS OF 5aza CdR ON GROWTH AND DIFFERENTIATION OF THE HUMAN LEUKEMIC CELL LINE U-937

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U-937 cells are susceptible of terminal differentiation once treated with six repeated pulses of 0.1 pM 5-aza-2'-deoxycytidine (5 azaCdR) administered every 12 hours [1]. In order to ascertain whether differentiation was dependent on the total dose of drug administered or was the result of a combination of 5aza CdR and time elapse, we analyzed growth and differentiation in 5azaCdR-treated U-937 cells after each pulse, at a final time point (72 hours) which was identical for all inductions. Results showed that only two pulses of 5azaCdR are sufficient to induce a dramatic decrease in DNA methylation (evaluated as DNA methylcytosine content) along with a permanent inhibition of colony formation by cells plated in 0.8% methylcellulose and a decrease in ^{3}H-thymidine uptake. On the contrary, administration of all the six pulses of 5azaCdR was needed to achieve cell differentiation in terms of % of NSE+ve polykarion-macrophage cells and % of CD31 and CD36+ve cells. We also reported that 5azaCdR-mediated differentiation of U-937 cells is accompanied by an early (within 12 hours) down regulation of *c-myc* expression, and a late induction of differentiation-related genes such as *c-fos, c-fins* and *c-fes*. Results *in vitro* parallel observations made in phase I-II trials using 5azaCdR[2,3] or 5azaCR [4] in AML [2] or MDS[3,4] in which a prolonged exposure to treatment (3 to 7 days) was required for effects to be detected clinically. Our hypothesis is that different metabolic pathways are affected by 5azaCdR and that a wary planning of administration is required to define the optimal administration schedule and final goal of leukemia treatment by differentiation inducers.

1. Attadia V. Leukemia 1993; 7, *Suppl. Monograph* 1:9-16.
2. Petti M.C., Mandelli F. *et al,ibid* 36-41.
3. Zagonel V., Lo Re G. *et al, ibid* 30-35.
4. Silverman L.R., Holland J.F. *et al. ibid* 21-29.

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182

RESISTANCE TO ALL-*TRANS* RETINOIC ACID THERAPY IN ACUTE PROMYELOCYTIC LEUKEMIA: *IN VITRO* STUDIES

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All-*trans* retinoic acid (ATRA) is an effective agent (45 mg/m^2/d) for inducing complete remission (CR) in patients with acute promyelocytic leukemia (APL) characterised by a distinct cytologic morphology (AML3 subtype), high incidence of coagulopathy and specific chromosomal translocation t(15;17) involving the alpha retinoic acid receptor on chromosome 17 and the PML gene on chromosome 15.

Unfortunately, we have observed the appearance of relapse if ATRA was continued as sole maintenance therapy after obtention of CR (median 5 months) and when these relapses occurred, ATRA failed to induce a second CR. We have investigated whether specific features of the AML3 cells at relapse could explain the *in vivo* resistance observed. AML3 patients' cells at relapse showed high levels of CRABPII, a cytosolic retinoic acid binding protein, not detected prior to ATRA therapy (PAGE technique). Moreover, relapse-AML3 cells (n=12) showed reduced differentiation (NBT test) induction when compared with "virgin"-AML3 cells.

Mechanisms of resistance involving ATRA hypercatabolism (induction of cytochrome P450-like enzyme systems and/or an increase of CRABPII) suggest the need for further studies on the appropriate doses (25 mg/m^2/d or less) and length of ATRA therapy in *de novo* and relapsing APL patients.

183