Low-Dose Cytarabine in Myelodysplastic Syndromes and Acute Leukemia

A Comment

E.	Elio	Cacciola
F.	Francesco	Di Raimondo
P.	Patrizia	Guglielmo
G.	Giuseppe	Milone
R.	Rosario	Giustolisi

Elio Cacciola, MD, Francesco Di Raimondo, MD, Patrizia Guglielmo, MD, Giuseppe Milone, MD, Rosario Giustolisi, MD, Institute of Medical Semeiotic I and Hematology, University of Catania, Via S. Citelli No. 6, 1-95124 Catania (Italy)

We have read with interest the paper of A. Inbal et al. [1] and we would like to make some comments. There are a few unclear data. The authors reported in table II that patient No. 2 had a granulocyte count of $5.98 \times 10^9/l$ before treatment with low-dose cytarabine (LDC) and a granulocyte count of $5.28 \times 10^9/l$ after treatment. It is also reported that patient No. 1 did not have any abnormal chromosomal pattern. Nevertheless, in the 'Results' and 'Discussion' sections they asserted that '... in 3 patients (No. 1, 2, 3) with refractory anemia (RA) normal peripheral blood was obtained after one course of treatment'. But patient No. 2 had before treatment with LDC a granulocyte count of $5.98 \times 10^9/l$ and of $5.28 \times 10^9/l$ after treatment; is this a mistake? Furthermore, the authors reported in the 'Discussion': '... therapy with LDC was associated with beneficial responses in 5 of the 8 patients, 3 of whom (namely the first three ones showed in the table) achieved normal peripheral blood counts'. However, patient No. 2 had yet prior to treatment a normal granulocyte count, whereas platelet count and Hb level were low. With regard to patient No. 1 the chromosomal analysis was normal (see table II), but in the 'Discussion' (p. 73) the authors reported as follows: 'In our 3 patients with refractory anemia (namely patients No. 1, 2, 3), despite excellent responses to cytarabine, the bone marrow metaphases remained 100% abnormal'. But if patient No. 1 had a normal chromosomal pattern before treatment, how could one explain 100% of metaphases abnormal? Is this a mistake? In addition, we would like to comment some suggestions of the authors with regard to the mechanism of action of LDC which, in our opinion, appears to be conflicting. They firstly reported that the LDC regimen results in inducing a suppression of the leukemic clone, so allowing the suppressed normal hematopoietic one to mature. The authors later reported that the excellent response to cytarabine regards a differentiating effect on the leukemic clone, as demonstrated by the persistence of abnormal bone marrow metaphases. This could be the case in the patient with acute leukemia (even if one had a normal karyotype), but it is questionable in RA patients. In RA patients the percent of bone marrow blast cells is very small (5%); therefore, it is difficult to think that the myeloid maturative effect of LDC corresponds to a differentiative stimulus on 'leukemic clone' rather than on 'suppressed normal hemopoietic line'. The finding of a persistent abnormal chromosomal pattern after LDC does not seem enough to support this view because it might concern the persistence of residual leukemic cells. On the other hand, the

authors did not evaluate before and after LDC (either) in peripheral blood (or bone marrow) the behavior of the ratio of differentiated myeloid cells to blasts. This is a simple parameter which is reported [2,3] to be suitable for the evaluation either in vivo or in vitro of granulocyte maturation.

In conclusion, we believe that in RA patients, as reported by Inbal et al. [1], the excellent response to LDC, rather than being due to a differentiating effect on leukemic clone, could be a consequence of allowing normal marrow to differentiate. This latter effect could occur either spontaneously or by the cytotoxic effect of cytarabine on the leukemic blasts with consequent loss of their inhibitory activity on normal myeloid progenitors [4]. However, the employment of LDC regimen is of interest especially in the management of myelodysplastic syndromes, although its mechanism of action still remains debated [4]. We agree with A. Inbal et al. with regard to the good tolerance of the LDC regimen.

126

Cacciola/Di Raimondo/Guglielmo/Milone/Giustolisi/Shakali

References

- Inbal, A.; Januszewicz, E.; Rabinowicz, M.; Shaklai, M.: A therapeutic trial with low-dose cytarabine in myelodysplastic syndromes and acute leukemia. *Acta haemat.* 73: 71-74(1985).
- Di Raimondo, F.; Guglielmo, P.; Milone, G.; Cacciola, E., Jr.; Giustolisi, R.: Low-dose of ARA-C in chronic myeloid leukemia in blastic transformation. *Haematologica* 3: 274-275 (1985).
- Michalewicz, R.; Lotem, I.; Sachs, L.: Cell differentiation and therapeutic effect of low doses of cytosine arabinoside in human myeloid leukemia. *Leuk. Res.* 5: 783-790 (1984).
- Winter, J.N.; Variakojis, D.; Gaynor, E.R.; Larson, R.A.; Miller, K.B.: Low-dose cytosine arabinoside (ARA-C) therapy in the myelodysplastic syndromes and acute leukemia. *Cancer* 56: 443-449(1985).