Fludarabine, cytarabine and topotecan (FLAT) as induction therapy for acute myeloid leukemia in the elderly: a preliminary report

A complete remission (CR) was achieved in 60% of 20 consecutive elderly patients (median age 70 years) with acute myeloid leukemia after a single course of fludarabine, cytarabine and topotecan. Ten patients are in first CR after a median follow-up of 8 months. This regimen is well tolerated and suitable for most elderly patients.

Unfavorable biological characteristics and host-related factors adversely affect the prognosis of acute myeloid leukemia (AML) in the elderly. Despite patient selection, using the standard anthracycline-containing regimens, the CR rate seldom exceeds 50-60%.[1] Furthermore, the role of intensified chemotherapy in older individuals is still questionable.[2] Most studies focus on induction regimens designed to reduce toxicity with the aim of extending the chance of CR to the majority of patients. The combination of high-dose cytarabine (Ara-c) and fludarabine (FLAG regimen) is active in patients with high-risk AML[3] and may constitute a suitable option in the elderly.[4] Recently, encouraging results were reported with intermediate-dose Ara-c plus topotecan in both myelodysplastic syndrome (MDS) and AML with unfavorable karyotype.[5] Thus we opened a pilot study combining fludarabine at a lower dose,[6] Ara-c and topotecan (FLAT) as induction treatment for elderly AML patients. Fludarabine 15 mg/m^2/d was given for 4 days i.v. in 0.5 hrs, followed 4 hrs later by Ara-c 2 g/m^2 i.v. over 4 hrs and topotecan 1.25 mg/m^2 i.v. over 4 hrs. After a single course, patients in CR received consolidation with both idarubicin 10 mg/m^2 and etoposide 175 mg/m^2 for two days, while those not in CR underwent salvage therapy. Twenty out 22 elderly non-M3 AML patients consecutively referred to our Department from July 1999 entered the study. It is noteworthy that, because of associated diseases or poor prognostic score, only 8 of them fulfilled the commonly applied eligibility criteria for a clinical trial with conventional chemotherapy. CR was achieved in 12 patients after a single FLAT course (Table 1). Among those not in CR after the first course, two were salvaged with the ICE regimen, so that the final CR rate was 14/20 (70%). A preceding MDS had no impact on CR achievement while the impact of an unfavorable karyotype did not reach statistical significance because of the small number of patients. Although very preliminary, these results are encouraging and appear mainly related to the negligible toxicity of the regimen: the planned post-induction treatment, either as consolidation or salvage therapy, was able to be applied to all patients. Transfusion support was constantly required with a mean of 9 red blood cell and 21 platelet units from random donors being given. Growth factors were given after chemotherapy only in the case of febrile neutropenia. Three infections were documented (2 pneumonia, one fatal sepsis by *Tricosporum begelii*); 4 patients had fever of unknown origin (median 2 days), none experienced significant hepatic or renal toxicity. The mean time from the end of therapy to a neutrophil count >0.5 and platelet count >20×10^9/L was 17 days. In October 2000, after a median follow-up of 8 months, 5 patients are dead and 15 alive. Three relapsed after 12, 8 and 5 months; 10 are in first CR (one patient died in consolidation). This induction regimen appears to be effective, well tolerated and suitable for most elderly patients. Moreover, the cost of one course of topotecan (5 mg/m^2) is comparable with that of other agents which must be given at higher doses. The follow-up is still inadequate to draw any conclusion about CR duration and survival. Randomized studies versus an anthracycline-containing regimen are advisable.

Table 1. Patient characteristics and clinical results (n=20).

M/F		10 / 10
Median age (range)		70 (60-81)
De novo/s-AML		14 / 6
M1-M2		6
M4-M5		14
Karyotype (19 performed)		
	Low risk	1
	Intermediate	11
	High risk	7
Results after one course:		
	CR	12 (60%)
	NR	7
	ID	1
CR: *de novo*		7 (50%)
	s-AML	5 (83%)
	≤ 70 yrs	6 (54%)
	>70 yrs	6 (67%)
	High risk karyotype	3 (43%)
	Low/intermediate	8 (67%)

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