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RESEARCH ARTICLE

Results of treatment of acute myeloid leukemia and myelodysplastic syndrome with etoposide, thioguanine, cytarabine (ETC) in elderly patients

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ABSTRACT

Treatment in elderly patients with acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) remains controversial, and results have been poor with most regimens. In order to study the efficacy of a new regimen in the treatment of these diseases in elderly patients assessed as not tolerating full-scale anthracycline-containing intensive chemotherapy, 14 patients over 60 years were enrolled in our study. The median age was 69 years, range 60-85 years. Eight patients had MDS (one transformed to AML) and six had AML.

Anthracycline-lacking therapy (ETC) consisted of etoposide 120 mg/m^2 and thioguanine 100 mg/m^2 p.o. twice daily on days 1-5 and cytarabine (araC) 40 mg/m^2 s.c. on day 1. The preliminary results were as follows: 7 of the 14 patients (50%) achieved complete remission. The median survival was 10 months. Days spent at hospital were 28. Neutropenia was observed for 11 days and thrombocytopenia for 15 days. No severe infection was detected. Early death was observed in 2 (14%) of the patients. In conclusion, this novel treatment with a complete response of 50% appears to be a simple, safe, cost-effective form of therapy for elderly patients.

Key Words: Acute myeloid leukemia, myelodysplastic syndrome, elderly patients

ÖZET

Yaşlı akut myeloid lösemili ve myelodisplastik sendromlu hastalarda etoposid, thioguanin, sitarabin tedavisinin sonuçları

Akut myeloid lösemili (AML) ve myelodisplastik sendromlu (MDS) yaşlı hastaların nasıl tedavi edileceği halen tartışmalıdır ve pek çok rejimle elde edilen sonuçlar olumsuzdur. Tam doz antrasiklin içeren yoğun tedavileri tolere edemeyecek 60 yaş üzerindeki 14 vakayı tedavi rejiminin etkinliğini göstermek için çalışmamıza aldık. Ortalama yaş 69 idi ve 60 ile 85 arasında değişmekte idi. Sekiz hastada MDS (biri AML ye dönüştü), 6 tanesinde de AML vardı.

Tedavi etoposid 120 mg/m^2 ve thioguanin 100 mg/m^2 p.o. günde iki kez 1-5.günler ve araC 40 mg/m^2 s.c. 1. günde verildi (ETC). Çalışmanın ilk sonuçlarında; on dört hastanın 7sinde (%50) tam yanıt elde edildi. Ortalama yaşam süresi 10 aydı. Hastanede geçirilen ortalama günler 28 gündü. Ortalama nötropeni süresi 11 gün iken trombositopeni süresi 15 gündü. Ciddi hiçbir enfeksiyon tespit edilmedi. Erken ölüm 2 (%14) hastada izlendi. Sonuç olarak bu yeni tedavi yaklaşımı yaşlı hastalarda %50'lik tam yanıt oranı ile basit güvenli ve ekonomik bir tedavi seçeneğidir.

Anahtar Sözcükler: Akut myeloid lösemi, myelodisplastik sendrom, yaşlı hastalar

INTRODUCTION

Forty percent of patients with acute myeloid leukemia (AML) are over 65 years of age and one-third are over 70 [1]. Myelodysplastic syndrome (MDS) is unusual in persons younger than 50 years of age [2]. Although aging is a highly individual process, elderly patients generally have delayed renal excretion of drugs and a higher incidence of treatment-related morbidity and mortality from aggressive chemotherapy comprising full-dose antileukemic drugs [3,4]. Some investigators have favored a mild chemotherapeutic approach while others have treated elderly patients with almost the same intensity as patients below the age of 60 years. In a randomized trial, the European Organization for Research and Treatment of Cancer and Leukemia Group (EORTC) has shown that the "wait-and-see and mild chemotherapy approach" resulted in a shorter median survival duration compared to more intensive treatment, 11 vs 21 weeks, respectively [5]. Although there were an appreciable number of complete remissions, there were also reports of great toxicity of the treatment [6,7]. Like this trial, most of the regimens contain anthracyclines, which results in cardiotoxicity especially in the elderly patients [8,9].

MATERIALS and METHODS

Patients over the age of 60 years with a newly diagnosed AML or MDS were evaluated for enrollment into the study. The study began in January 2001 and the last included patient entered the study in mid-September 2004. Long-term follow-up in mid-September was at ≥3 years. All patients signed consent forms and the study was performed in accordance with the Declaration of Helsinki. All patients were previously untreated. Genetic study was performed in only five of the patients and they had favorable outcomes (3 with normal cytogenetics, 2 with deletion of 5q). Treatment (ETC) comprised etoposide 120 mg/m² and thioguanine 100 mg/m² twice daily orally on days 1-5, and cytarabine (ara-C) 40 mg/m² s.c. twice daily on day 1. Patients were given two cycles of the chemotherapy. If no complete remission (CR) was achieved after two courses of therapy, further treatment was optional. Bone marrow aspiration biopsies were performed on the 14th and 28th days. Criteria for CR were a normocellular bone marrow, <5% blast cells present in bone marrow, no dysplastic changes, ≥25% normal myelocytes, metamyelocytes, and granulocytes with rod–segmented nuclei in bone marrow, normal blood hemoglobin values, and platelet counts > 150 x 10^9/L.

RESULTS

SPSS version 11.0 was used for statistical analysis. Kaplan-Meier was used for the evaluation of survival**.** Table 1 summarizes the clinical details of patients, including response to treat-

Table 1. Summary of clinical details

Patient	*Age(yr)*	*Sex*	*Diagnosis (post)*	*Response to treatment*	*Early death*	*Duration of remission (mo)*	*Duration of survival (mo)*
1	72	F	MDS (RAEB2)	CR	∅	9	41
2	67	M	MDS (RAEB2)	PR	∅	3	4
3	67	F	AMLM1	CR	∅	5	5a
4	60	F	MDS (RAEB2)	PR	∅	9	9a
5	63	F	AMLM2	CR	∅	8	16
6	82	F	MDS (RAEB2)	CR	∅	7	13
7	72	M	MDS (RAEB2)	CR	∅	8	13a
8	74	M	AMLM2	NR	+	nil	1
9	85	F	AMLM2	PR	∅	5	6
10	68	F	AMLM2	NR	+	nil	1
11	60	M	AMLM2	CR	∅	1	2
12	66	M	MDS--AML	NR	∅	1.5	16
13	77	F	MDS (RAEB2)	PR	∅	3	4
14	68	M	MDS (RAEB2)	CR	∅	11	19

AML: Acute myeloid leukemia according to the French–American–British (FAB) classification. **RAEB 2:** Refractory anemia with excess blasts according to WHO classification. **CR:** Complete remission (<5% blasts in bone marrow). **PR:** Partial remission (6-15% blasts). **NR:** No response.
a: Still alive.

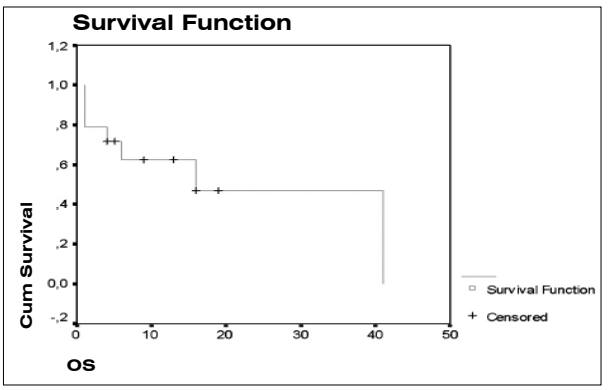

Figure 1. Overall survival among all patients registered in the study.

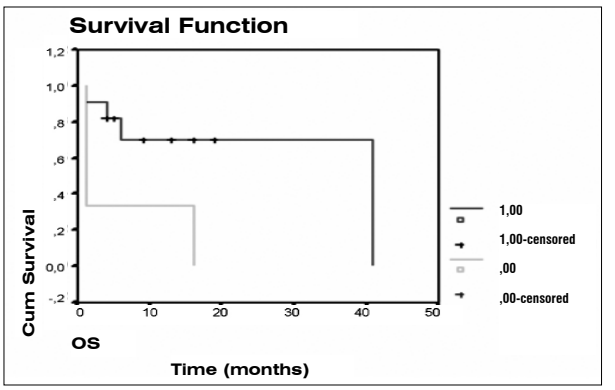

Figure 2. Survival among the responders and non-responders to treatment.

ment and duration of survival. CR was achieved in 7 of 14 patients (50%) and partial remission (PR) in 4 patients (35%). Overall response was observed in 11 patients (78%). In those with CR, it was achieved in the first course of the treatment. Treatment was well tolerated by all patients. Myelotoxicity and pancytopenia occurred regularly, with time to recovery (neutrophils ≥ 0.5 x 10^9/L, platelets ≥ 50 x 10^9/L) from nadir 11 days and 15 days, respectively. There was no need for colony stimulating factors. At the time of the analysis, three patients had survived. The survival is presented in Figure 1. The median survival was 10 months. Figure 2 shows the survival among the responder and non-responder patients to treatment. Early death (i.e. death within 30 days of treatment) was observed in two of the patients (14%) due to acute renal failure and gram negative septicemia in patients 8 and 10, respectively. The mean need for transfusion was limited to 3 apheresis units of thrombocytes and 4 units of erythrocytes. Patient number 3 had no need of transfusion during treatment. Mean time of hospitalization was 28 days (range 25 to 47 days).

DISCUSSION

This trial attempted to evaluate ETC treatment for AML and MDS in elderly patients. Although the number of patients in this study is small, the results appear to vindicate our hypothesis. In fact, the overall response rate of 78% is better than those reported with low dose ara-C (54%) or intensive therapy (54%) [10], and it is the same as the study with low-dose ara-C, etoposide, and mitoxantrone or thioguanine (78%) [11]. The duration of survival in the 11 responding patients ranged from 2+ to 41+ months, whereas it was between 1+ to 16+ months in the non-responding patients. Most of the regimens used in elderly patients contain anthracyclines. In the study reported by Ruutu *et al.* [12], 92 patients were treated with etoposide 80 mg/m², thioguanine 100 mg/m² PO bid for 5 days, thioguanine 100 mg/m² and idarubicin 12 mg/m². Mean age was 72 years (range 65-84 yrs). Median survival in the responding patients was 10 months. The frequency of CR is comparable to that in other studies using a daunorubicin, ara-C, thioguanine regimen with general CR rates of 52-58% [6,13,14] and of 25% in patients above 70 years of age [15]. In a Danish study of AML, aclarubicin in combination with ara-C resulted in a CR rate of 47% in the cases between 61-65 years of age [16]. Thus, the CR rates are similar to the 50% CR rate of our trial.

Our regimen does not contain anthracyclines and can be used in cases with poor cardiac performance status. When we consider the mean age of 69 in our study, a 50% CR rate with no anthracycline is a favorable result. In the present study, days spent at hospital were reduced (median time spent at hospital was 4 wks, and the number of infusion days was also markedly reduced), and a less-toxic regimen, without compromising the antileukemic effect, was achieved. The number of days with neutropenia and thrombocytopenia was small. We did not perform a formal quality of life assessment, but the few infusion days, and no more side effects than with intravenous treatment, suggest better quality of life when oral consolidation was used. Since the outcome of AML and MDS in the elderly is unsatisfactory with the treatments currently in use and better treatments are needed, oral treatment with ETC, in the present situation, may be an alternative regimen in the management of elderly patients with AML and MDS, especially in those with cardiac problems.

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