Long Term Low Dose Maintenance Chemotherapy in the Treatment of Acute Myeloid Leukemia

Murat TOMBULOĞLU*, Seçkin ÇAĞIRGAN*

* Department of Hematology, Faculty of Medicine, Ege University, İzmir, TURKEY

ABSTRACT

In this study the effect of low dose long-term maintenance chemotherapy in patients with acute myeloid leukemia (AML) was evaluated. Following a complete remission two consolidation courses were given with the same drugs. Thereafter patients received low dose maintenance chemotherapy in every four weeks until disease relapsed or for up to two years. A total of 68 patients were evaluated. The median duration of remission of 22.5 months in patients who received maintenance chemotherapy while it was only 7 months in those without maintenance chemotherapy after a median follow-up time of 71 months, which was significant. Overall survival (OS) was also significantly longer in patients with maintenance therapy. Similar results were also obtained in comparison of patients over 60. Thus, it was concluded that maintenance therapy might be beneficial for older AML patients with limited therapy choice.

Key Words: Acute myeloid leukemia, Maintenance chemotherapy.

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INTRODUCTION

Standard induction chemotherapy of AML produces a complete remission in 60 to 70% of adult patients[1]. Without postremission therapy, remission duration is very short (mean 4-8 months) and less than 5% of patients are disease free in 5 years[1,2]. However, bone marrow transplantation and high dose consolidation chemotherapy prolongs both remission duration and survival[3,4]. When intensive chemotherapy is administered for elderly patients with AML there was an increase in induction deaths associated with infection and other toxicities. Since AML predominantly occurs in elderly, the majority of patients cannot tolerate these forms of therapies.

The positive role of maintenance chemotherapy has not been demonstrated in patients with AML. In this retrospective study the effect of long-term low dose maintenance chemotherapy on remission duration and survival was investigated.

PATIENTS and METHODS

Between December 1991 and December 1996, sixty-eight patients with AML who showed first complete remission after a standard induction chemotherapy were evaluated. Eligibility criteria were age (> 15 years) and bone marrow diagnosis of AML by aspiration and/or biopsy based on FAB classification. Patients with AML M_3 and patients who did not show a complete remission after two courses of induction therapy were excluded. Characteristics of patients are shown in Table 1. Remission induction therapy consists of thioguanin 80 mg/m^2 orally twice daily on days 1 through 7 plus cytarabine 100 mg/m^2 IV over 2 h in every 12 h on days 1 through 7 plus daunorubicin 60 mg/m^2/day by intravenous bolus on days 1, 2 and 3 (TAD 7/3). A second identical course of therapy was given to patient who did not show a complete remission after the first induction. Patients who achieved a complete remission were given two cycles of consolidation therapy consisting of the same drugs for 5 days with thioguanine and cytarabine and 2 days with daunorubicin (TAD 5/2).

Daunorubicin dose was reduced to 30 mg/m^2/day in patients older than 60 years old. Maintenance therapy consisted of thioguanine 80 mg twice daily, per orally for 4 days and cytarabine 100 mg IV short infusion on day 5. The courses were repeated every four weeks until disease relapsed or for up to 2 years.

Distributions of leukaemia free survival and overall survival were estimated by the product limit method. The Logrank test used for comparison. Statistical analyses were done by Prism Software (Graph Pad Software Inc. San Diego, USA).

RESULTS

All patients tolerated maintenance therapy well and no major toxicity occurred. None of the patients was hospitalised due to maintenance chemotherapy. The median duration of remission of 22.5 months in patients who received maintenance chemotherapy while it was only 7 months in those without maintenance chemotherapy after a median follow-up time of 71 months (range, 40-86 months), which was significant. Probabi-

Table 1. Patient characteristics

	Maintenance	No maintenance	Total
No of patients	30	38	68
> 60 years	11	7	18
Sex (male/female)	12/18	21/17	33/35
Age (years)	50 (range 17-72)	42 (range 19-76)	45 (range 17-76)
FAB subtypes			
M_1	4	12	16
M_2	18	10	28
M_4	4	8	12
M_5	2	7	9
M_6	1	-	1
M_7	1	1	2

lity of leukemia-free survival (LFS) at 5 years was 26% for patients receiving maintenance chemotherapy and 0% for patients without this therapy (Figure 1). OS estimates were also significantly different between the groups (32% and 10% at 5 years) (Figure 2).

For patients older than sixty with a median follow up of 77 months, probability of LFS at 5 years was 9% in therapy given group while it was 0% those without maintenance chemotherapy. That was also statistically significant (Figure 3). OS was also significantly longer in patients with maintenance therapy (18% and 0% at 5 years) (Figure 4).

DISCUSSION

In recent years results of treatment for AML has improved with the identification of groups of patients with different prognosis and the development of risk-directed treatment strategies. Increasing age and the presence of unfavourable cytogenetic abnormalities are poor prognostic factors[5]. In wes-

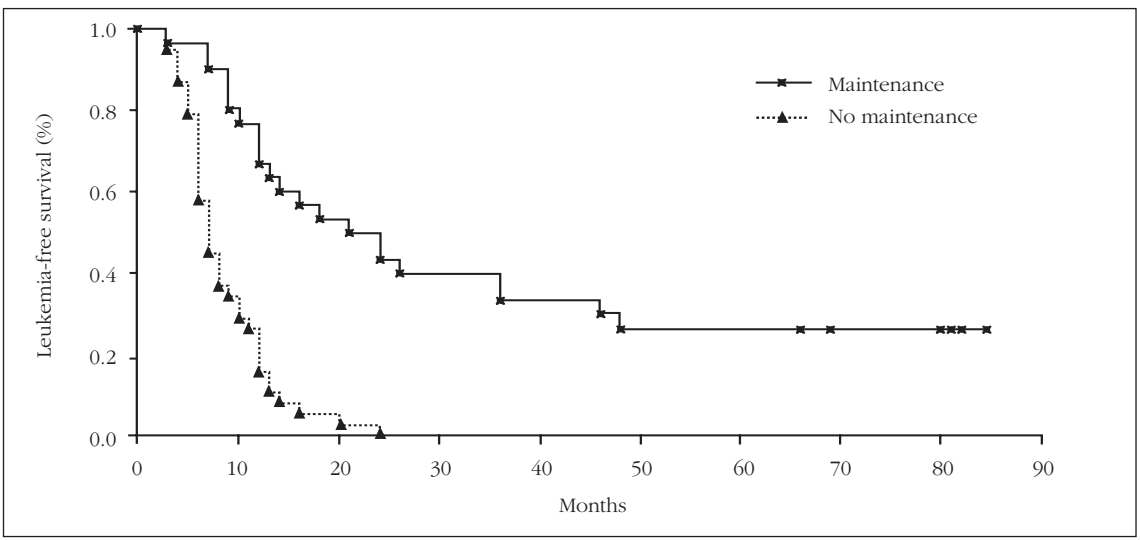

Figure 1. Kaplan-Meier analysis of the two groups (Logrank test, p< 0.0001).

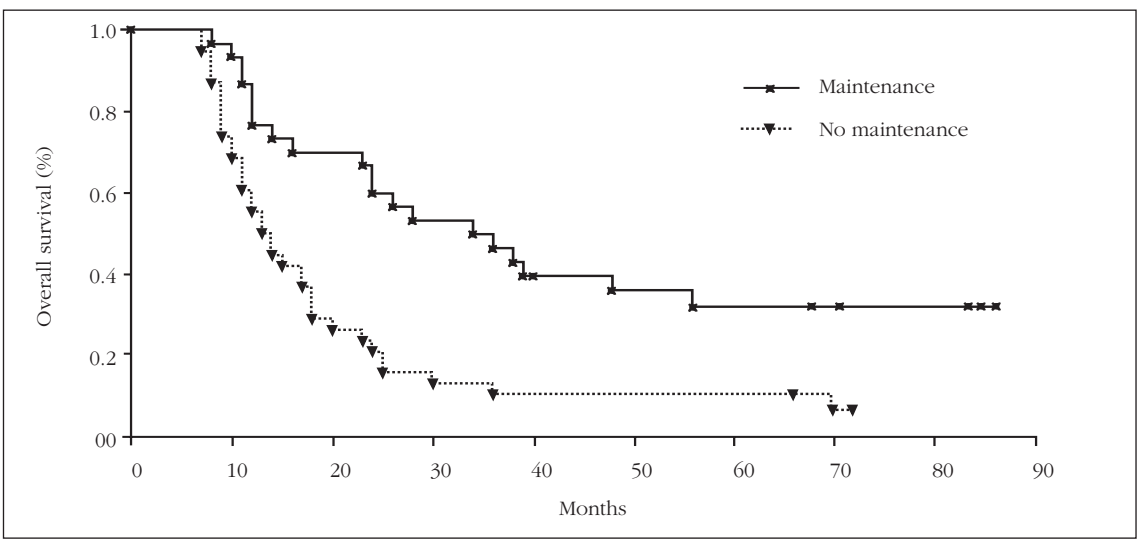

Figure 2. Kaplan-Meier analysis of the two groups (Logrank test, p= 0.0005).

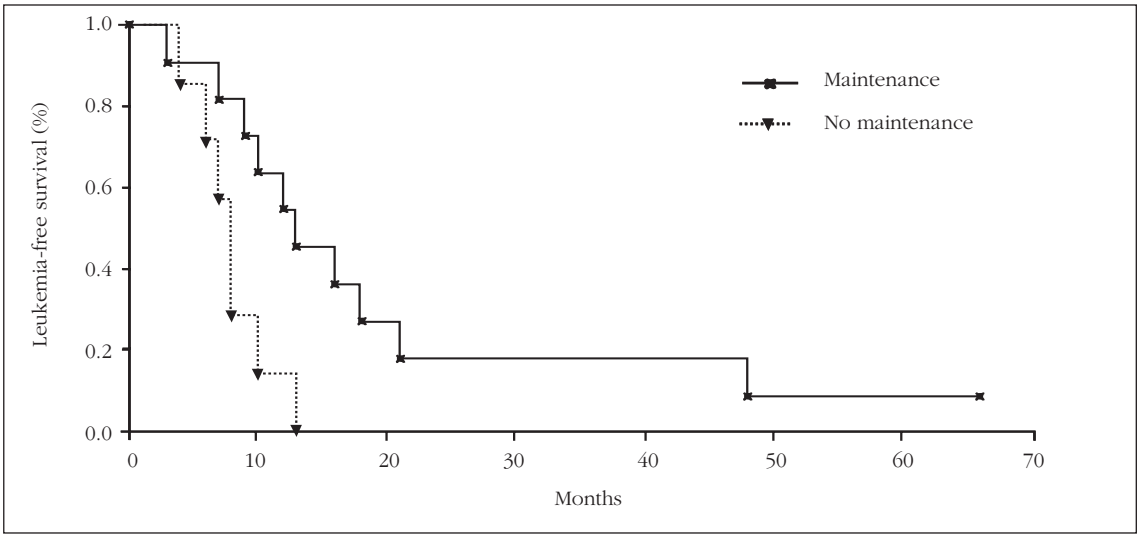

Figure 3. Kaplan-Meier analysis of two groups of patients older than 60 (Logrank test, p= 0.018).

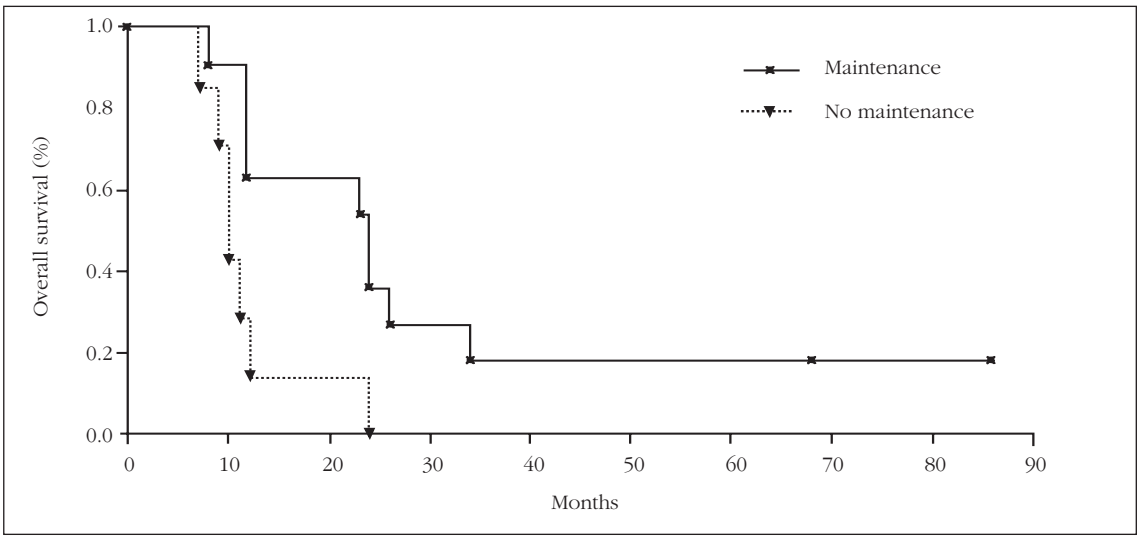

Figure 4. Kaplan-Meier analysis of two groups of patients older than 60 (Logrank test, p= 0.008).

tern countries more than 70% of AML patients are older than 50 years old. In elderly patients (> 60 years) remission duration is shorter and toxicity of chemotherapy is higher compared to younger patients. Induction chemotherapy has been considered inadequate without consolidation and there is nearly no long-term survival. Elderly patients can not tolerate allogeneic bone marrow transplantation or high dose post remission consolidation chemotherapy.

The role of low dose maintenance therapy especially in elderly patients is not known. Büchner et al reported 28% long-term remission with 3 years maintenance therapy in AML patients older than 60 years old[6]. In contrast, a randomised study did not show any difference between short (8 months) or long (36 months) maintenance therapy in respect to long-term survival[7]. Another study has showed that long-term daily low-dose cytosine arabinoside prolongs remissi-

on and relapse rates have increased after withdrawal of therapy[8]. 100 mg/m^2 oral busulphan could provide similar survival rates and low toxicity with respect to bone marrow transplantation in AML patients older than 50[9]. In a recent randomised collaborative study of phase III EORTC and HOVON groups low dose cytarabine for maintenance therapy prolonged disease free survival but not total survival in patients older than 60 years old[10]. However, in our study LFS and OS durations increased in patients both over and below sixty. Therefore, maintenance therapy might be recommended for older patients with limited choice of therapy since younger patients could get benefit from other forms of treatment.

In conclusion this study suggests low dose long term maintenance therapy can be a safe and effective therapy in older AML patients.

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Address for Correspondence:

Murat TOMBULOĞLU, MD

Department of Hematology
Faculty of Medicine
Ege University
35100, Bornova, İzmir, TURKEY