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Mobilization-Driven Postconsolidation Therapy in Elderly Patients with Acute Myeloid Leukemia: Feasibility and Efficacy of Autologous Stem Cell Transplantation versus Low-Dose Gemtuzumab Ozogamicin

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A B S T R A C T

We prospectively evaluated 2 postconsolidation strategies, administered according to the mobilization outcome, in 72 acute myeloid leukemia (AML) fit elderly patients, achieving complete remission after the first high-dose cytarabine-based induction. Autologous stem cell transplantation (ASCT) was performed in patients collecting $\geq 3 \times 10^6$ $CD34^+$/kg and low-dose gemtuzumab ozogamicin (GO) was performed in poor mobilizers (collecting $<3 \times 10^6$ $CD34^+$/kg). Fifty-five patients (76.3%) underwent peripheral blood stem cell (PBSC) mobilization, after first consolidation, and 24 of 55 (44%) collected $>3 \times 10^6$ $CD34^+$ cells/kg. Among the 55 patients eligible for PBSC mobilization, 7 did not receive the planned treatment, 23 were allocated for ASCT, and 25 were allocated for GO on an intention-to-treat basis. With a median follow-up of 70 months (range, 24 to 124), 20 of 55 patients are alive, 18 of them in continuous complete remission. The 8-year overall survival (OS) and disease-free survival (DFS) are, respectively, 35.9% (95% confidence interval [CI] 24% to 49.8%) and 31.2% (95% CI, 21% to 43.8%), median OS and DFS were 22 and 16 months, respectively. In multivariate analysis, postconsolidation treatment and hyperleukocytosis (WBC > 50,000/μL) significantly predicted OS and DFS, whereas secondary AML was significantly associated with a higher relapse rate (83.4% versus 54% of de novo AML). Patients with hyperleukocytosis had 0% 3-year OS versus the 46% (at 8 years) in patients without hyperleukocytosis ($P = .01$); 57% of patients in the GO arm are alive at 8 years, compared with 25.4% of patients in the ASCT arm, who had an overall relative risk (RR) of death of 2.6 (95% CI, 1.2 to 5.8; $P = .02$). DFS at 8 years was 45.3% in patients receiving GO, compared with 26% in ASCT arm (RR, 2.1; 95% CI, 1 to 4.3; $P = .05$). Our study outlines low feasibility and efficacy of ASCT in elderly AML patients, whereas postconsolidation with GO appears safe and effective in this unfavorable setting. The study was registered at Umin Clinical Trial Registry (www.umin.ac.jp/ctr), number R000014052.

INTRODUCTION

Acute myeloid leukemia (AML) in elderly patients is still characterized by poor prognosis. Factors related to age, including poor performance status (PS) and comorbidities, may negatively affect tolerance to treatment [1].

In this setting, the high frequency of secondary AML, often associated with multidrug resistance phenotype and/or unfavorable karyotype, may likewise lower the response rate and response duration [2]. Despite the introduction of new drugs, no significant improvement has been observed in recent years in this setting [3]. The intensification of induction with high-dose daunorubicin has been explored, only in patients under 65 years, with encouraging results [4]. High-dose cytarabine (HD-ARAC) has also been tested as consolidation treatment in younger patients, but this approach has been discouraged in the elderly population [5,6]. The poor outcome in these older patients is generally

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characterized by a low complete remission (CR) rate and a high treatment-related mortality (TRM) rate, but it also yields an unacceptably high relapse rate. This is not only due to the adverse biological features of the disease, but also by the inefficacy (and/or low feasibility) of the post-consolidation therapy. A large German multicenter trial in patients ages 16 to 85 years did not show a better outcome after autologous stem cell transplantation (ASCT), compared with maintenance therapy [7]. However a number of trials, including ASCT as postconsolidation strategy in elderly AML patients, show low percentages of patients receiving this kind of postconsolidation strategy [8-10].

Gemtuzumab ozogamicin (GO) is an anti-CD33 humanized monoclonal antibody, conjugated with calicheamicin [11]. This antibody has been used at conventional dose (9 mg/m^2) in combination with induction chemotherapy in AML elderly patients, achieving an overall and relapse-free survival advantage [12,13]. Conversely, the Hemato-Oncology Cooperative Hovon Group/Swiss Group for Clinical Cancer Research (HOVON-SAKK) randomized trial failed to show a significant better outcome, administering GO at 6 mg/m^2 as postconsolidation treatment [13]. The recent Medical Research Council (MRC) study showed that adding GO to the induction schedule was associated with a better outcome, especially in patients with favorable-intermediate cytogenetic/molecular markers [14].

Except for some preliminary data suggesting the feasibility of GO at very low dose as postconsolidation therapy [15,16], so far this drug has never been investigated in this setting. To offer an alternative post-consolidation treatment to the elderly AML patients, fit for ASCT, failing PBSC mobilization, we designed a post-consolidation schedule with GO at very low dose, in order to evaluate the feasibility and efficacy of these two different post-consolidation therapies. Patients were enrolled in the two treatment arms according the mobilization outcome, and results were analysed on an intention-to-treat basis.

PATIENTS AND METHODS

This is a phase II prospective study, conducted in fit elderly AML patients in CR1, after intensive induction therapy, based on the association of idarubicin with HD-ARAC, as previously reported [17]. The main objective was to assess feasibility (in terms of safety and efficacy) of 2 postremission strategies: ASCT and low-dose GO. The primary endpoint was to evaluate overall survival (OS) in the 2 cohorts; secondary endpoints were treatment-related mortality (TRM), relapse incidence (RI), and disease-free survival (DFS).

The study was approved by the institutional review board and registered in the UMIN Clinical Trial Registry (R000014052); all patients gave written informed consent in accordance with the Helsinki declaration. Among 100 non-M3 AML fit elderly patients, ages >59 years, receiving intensive induction, 72 achieved CR after induction treatment and 55, who maintained first continuous complete remission (CCR) after first consolidation, received filgrastim (5 μg/kg per day subcutaneously from day +1 after the end of chemotherapy until the last leukapheresis) for PBSC mobilization. Collection of CD34$^+$ cells and ASCT management were performed as previously described [18]. A minimum dose of CD34$^+$ cells collected (>3 × 10^6/kg) was required for ASCT. The minimum CD34$^+$ cell dose required for ASCT was increased from the usual target of 2 × 10^6/kg to 3 × 10^6/kg because we were aware of an incomplete or slow hematological recovery in this elderly AML setting. According to the mobilization outcome, patients were analyzed either in the ASCT arm (CD34$^+$ collection ≥3 × 10^6/kg) or in the GO arm (CD34$^+$ collection <3 × 10^6/kg), regardless of the treatment they actually received on an intention-to-treat (ITT) basis. The ASCT procedure was performed in hospitalized patients and the supportive care, including antimicrobial prophylaxis, has been previously described [18]. The first 12 patients underwent a conditioning regimen including melphalan at 120 mg/m^2 i.v., associated with oral busulfan (9.6 mg/kg). However, because of a high incidence of severe mucositis, the protocol was amended replacing the former conditioning regimen with a BEAM modified scheme including 140 mg/m^2 melphalan i.v., associated with bis-chloroethylnitrosourea (BCNU) (300 mg/m^2), cytarabine 2400 mg/m^2, and etoposide 450 mg/m^2 in 9 further patients; patients over 70 years of age received the same schedule with 30% reduction of the drug dosage.

In patients collecting <3 × 10^6/kg CD34$^+$, not eligible for ASCT, GO was administered on outpatient basis at 3 mg/m^2 i.v., every 28 days for 3 months, followed by 3 infusions at 3-month intervals. The study flowchart is illustrated in Figure 1. The main clinical and biological characteristics of the AML

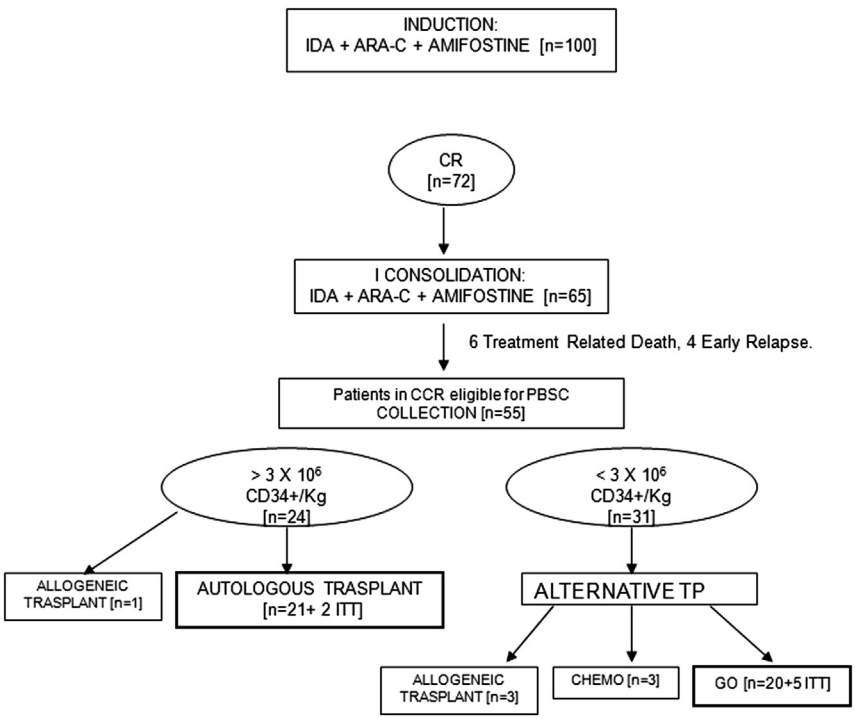

Figure 1. Flow chart of the study design and patients' treatment.