Induction therapy of AML with ara-C plus daunorubicin versus ara-C plus gemtuzumab ozogamicin: a randomized phase II trial in elderly patients


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Background: Chemotherapy for elderly patients with acute myeloid leukemia (AML) results in a median overall survival (OS) of ≤1 year. Elderly patients often present with cardiac comorbidity. Gemtuzumab ozogamicin (GO) is active in elderly (≥60 years) patients with relapsed AML with low cardiac toxicity.

Patients and methods: This randomized phase II study compared a standard combination of ara-C and daunorubicin (DNR; 7+3) versus ara-C plus gemtuzumab ozogamicin (7+GO) as the first course of induction therapy. Primary objectives were comparison of blast clearance on day 16, event-free survival (EFS), and remission duration. OS, complete remission (CR), and tolerability were secondary objectives.

Results: One hundred and nineteen patients with de novo AML, treatment-related AML, AML with a history of myelodysplastic syndrome (MDS), or high-risk MDS entered the study. Median age of 115 patients (intent-to-treat population) was 69 years. Protocol outlined a second course 7+3 for patients without blast clearance and two courses of high-dose ara-C consolidation upon CR. Both treatments were equally effective in blast clearance, CR, EFS, remission duration, or OS (median: 7+3, 9 months; 7+GO, 10 months). Induction death rate was higher in the GO group due to veno-occlusive disease.

Conclusion: The study did not show significant superiority of 7+GO over standard 7+3.

Key words: AML in elderly, gemtuzumab ozogamicin, induction therapy, Mylotarg

Introduction

Treating older patients with acute myeloid leukemia (AML) continues to be an important challenge. While the age group of ≥60 years represents only approximately one-third of the patients included in large multicenter studies, they actually account for the majority of AML patients [1–3]. The unfavorable biology of this disease in the elderly and the increased incidence of relevant comorbidities leading to less intensive chemotherapy regimens are among the reasons for the poor prognosis in this age group despite antileukemic therapy [4]. Previous studies demonstrated dose-related therapeutic effects in patients >60 years, in particular for daunorubicin (DNR) in the induction treatment and for postremission therapy [5, 6]. Recent studies confirm the efficacy of high-dose DNR over lower doses in AML patients aged <60 [7] and ≥60 years [8], but the latter trial confirmed the poor prognosis for elderly patients with an overall survival (OS) ≤25% after 5 years. In addition, many older patients present with significant cardiac comorbidity rendering the use of nontargeted anthracyclines hazardous. The acridine derivative m-amsacrine (AMSA), a topoisomerase II inhibitor, has been proposed as a substitute for anthracyclines in such cases [9], and we have recently reported a matched-pair analysis showing no disadvantage using AMSA instead of DNR in combination induction chemotherapy [10].

Gemtuzumab ozogamicin (GO; Mylotarg) is a cytotoxic drug, calicheamicin, which is targeted to CD33-positive cells by an mAb, gemtuzumab [11]. Upon cellular uptake, the toxic component is released through pH-dependent lysis of the linker [11]. GO was approved in the United States for therapy of...
elderly patients with AML after relapse, which was based on phase II data [12, 13]. With the exception of veno-occlusive disease (VOD), the tolerability of the compound is good; there was no major concern about cardiovascular toxicity in the early trials [12, 13]. GO has been tested within a variety of studies with different dosing and schedules, but only few data from randomized studies were available when this trial was started [14]. However, within a considerable number of recent trials, only one reported cardiac toxicity using high doses of GO for induction, consolidation, and maintenance [15].

The hypothesis tested in the present study was that a cytotoxic drug targeted to hematopoietic precursor cells should have superior efficacy in comparison with a nontargeted anthracycline, when given as part of induction therapy to patients with AML, and that in a patient population ≥60 years of age the toxicity profile of GO is better than that of DNR. The purpose of this study was to test the possibility of replacing DNR by GO in the first cycle of induction in a randomized phase II trial and to generate data allowing a decision for a larger randomized study.

patients and methods

Due to study onset in 2005, it was not registered at clinicaltrials.com. The ‘study’ was registered with the German Kompetenznetz Leukämie (http://www.kompetenznetz-leukaemie.de/content/aerzte/studien/studienregister/) and the outline of the trial was published before, when the trial was actively recruiting [14]. The trial was conducted according to the German drug regulations (AMG); it was approved by the joint Ethical Board of the Physicians Chamber Westfalen-Lippe and the Faculty of Medicine of the Westilian Wilhelms University in Muenster and the Ethical Boards of the participating institutions. Written informed consent according to the Helsinki declaration of the patients was mandatory before entry on study.

The ‘study flow sheet’ including Consolidated Standards of Reporting Trials information is depicted in Figure 1. ‘Inclusion criteria’ were age ≥60 years, diagnosis of de novo or secondary AML with the exception of French–American–British (FAB) type M3, refractory anemia with excess of blasts in transformation according to FAB, and CD33 positivity. ‘Exclusion criteria’ were contraindications for combination chemotherapy (renal and hepatic insufficiency, heart insufficiency New York Heart Association III and IV) or uncontrolled infection. A therapeutic prephase with 100 mg/m²/day of ara-C as an i.v. infusion was allowed for early stabilization. Patients were randomized up front and, similar to the standard therapeutic regimen for induction treatment of AML patients ≥60 years used by the German AML Intergroup (Kompetenznetz Leukämie) at the time of this study, received a combination of ara-C (100 mg/m²/24 h i.v. as continuous infusion, days 1–7) and DNR (60 mg/m² i.v., days 3–5) (7+3) in the control arm, or ara-C (as above) and gemtuzumab ozogamicin (6 mg/m² i.v., day 1 and 4 mg/m² i.v., day 8) instead of DNR (7+GO), as the first induction chemotherapy cycle. Obligatory bone marrow evaluation was carried out on day 16 after treatment onset. Patients with <5% blasts on day 16 were discharged after clinical recovery and recovery of blood counts. Patients in the 7+3 control arm with ≥5% remaining blasts on day 16 obtained a second course of 7+3 on day 21 whenever clinically possible. Patients in the 7+GO arm with ≥5% remaining blasts were switched to an additional course of 7+3 on day 21 whenever clinically possible. When considerable increase of AML disease burden was diagnosed on day 16 as compared with baseline (blast count in the bone marrow), salvage therapy using high-dose ara-C combinations was allowed according to the German AML Cooperative Group (AMLCG) protocols [6]. Patients achieving complete remission (CR) obtained consolidation therapy administered as two courses of high-dose cytarabine (HD-ara-C; 1 g/m², q 12 h, days 1, 3, and 5) with 4 weeks of rest following discharge from hospital after the previous course.

‘Primary end points’ of the study were event-free survival (EFS), early treatment efficacy (bone marrow blasts <5% on day 16), and time to relapse/remission duration for CR patients. ‘Study secondary end points’ were CR rate, rate of complete remission without complete platelet or neutrophil regeneration (CRp/CRi), OS, toxicity according to the CTC-NCI criteria, duration of leukocytopenia, rate of death during induction, length of hospital stay, and quality of life (as evaluable). End points were defined as published [16]. Statistical analysis was carried out with the nonparametric Mann–Whitney test. Survival times were compared with the log-rank test. All displayed P values are two sided.

On the basis of the data from the AMLCG [4], the study was powered to detect an increase of median EFS from 90 to 160 days and a prolongation of the median OS from 9 to >16 months with a power of 80% (alpha = 0.05), in order to obtain information as a basis for potential further phase III randomized studies.

results

Overall, 119 patients entered the trial; recruitment period was from June 2005 until June 2009. Four patients had to be excluded (three in the 7+GO and one in the 7+3 arm) for violation of admission criteria (1× no AML, 2× withdrawal of consent at the time of inclusion, 1× death at randomization) leaving an intent-to-treat population of 115 patients with 57 patients randomly allocated to the 7+GO and 58 patients into the 7+3 arm (Figure 1). Intent-to-treat patient’s characteristics are given in Table 1. Both arms of the study were well balanced for the main prognostic criteria for AML (age distribution, type of AML, FAB subtype, performance score, cytogenetics, white blood cell (WBC) count, lactate dehydrogenase). Cytogenetic subgroups were defined as previously suggested [17–20]. Median ‘time of follow-up’ in this study at the time of evaluation was 33.4 months.

Short-term and long-term ‘toxicity’ in both groups were compared between the two arms (Table 2). There was no difference with reference to the times of grade IV leukocytopenia during induction, no cardiac toxicity, but an excess severe hepatic toxicity in the 7+GO group with three patients developing grade IV VOD and two patients dying from clinical complications based on VOD. We had planned to use prophylactic defibrotide; however, during the time of the trial this drug became unavailable. Induction resulted in death without information about leukemia status in eight versus three, death with persistent leukemia in two versus zero, and death without remaining leukemia in one versus zero patients in the 7+GO and the 7+3 group, respectively. Comparisons of these parameters did not show significant differences between the two arms of the study. However, taken together 11 versus 3 induction deaths resulted in a P value of 0.021 in favor of 7+3 induction. Causes of death were sepsis and pneumonia with no difference between the two arms of the study. Two of the patients dying in the 7+GO arm, however, had severe VOD as the underlying complication. In this study, two consolidation courses with HD-ara-C at the level of 1 g/m² were feasible. There were short recovery times for neutrophils and platelets.
Induction:
7+GO:
- d1: GO 6mg/m² i.v.
- d1-7: Cytarabine 100mg/m² c.i.
- d8: GO 4mg/m² i.v.
7+3:
- d3-5: Daunorubicin 60mg/m² i.v.
- d1-7: Cytarabine 100mg/m² c.i.

Consolidation:
2x HD Ara-C:
- d1,3,5: Cytarabine 1g/m² q 12h i.v.

(see Table 2) and we observed only one septic death during aplasia.

An overview of the primary ‘efficacy end points’ blast clearance and remission is provided in Table 3. Early blast clearance has been described as an independent prognostic factor for achieving CR and for long-term outcome in earlier AMLCG trials [21]. Complete blast clearance (<5%) in the bone marrow following the first induction cycle (day 16) was achieved by 15 patients (31.25%) in the 7+3 group and by 14 patients (29.17%) in the 7+GO group (P = n.s.). Only three patients (two in the 7+3 and one in the 7+GO arm) received salvage therapy with HD-ara-C regimen as second induction since increasing blasts were diagnosed on day 16. Thirty-one patients (54.39%) in the 7+GO group and 32 patients (55.17%) in the 7+3 group achieved a CR (P = n.s.). Two additional patients in the 7+GO group and three in the 7+3 group achieved blast clearance from bone marrow but not fulfilling criteria for CR due to low WBC and/or lack of platelet recovery (CRi/CRp). EFS and remission duration are shown in Figure 2. Although a trend in favor of 7+GO was observed in every evaluation, there was no significant difference between the two study arms (details not shown). Twenty patients in the 7+3 group and 13 in the 7+GO group were found with persistent leukemia upon induction (P = n.s.). The median OS was 9 months in the 7+3 group and 10 months in the 7+GO group with no significant difference between the treatment arms (see Figure 3). Also the relapse-free survival was without significant difference between the groups (see Figure 3).

discussion

Taken together, replacing DNR with GO (Mylotarg) as component of the first induction therapy of elderly AML patients did not significantly affect the primary efficacy end points of this study (EFS, day 16 blasts <5%, remission duration). Although there was a trend toward a better remission duration for the patients receiving 7+GO as the first course of induction therapy, we also observed excess toxicity during induction therapy with this regimen, partly due to VOD. Whereas cardiac toxicity was no problem, severe VOD occurred in ~10% in the 7+GO arm and two patients died due to this complication. This is a toxic side-effect known and attributable to GO [14]. It was not possible to give prophylactic defibrotide to prevent this toxicity throughout the study since this agent was not available. However, prophylactic defibrotide may be able to inhibit the occurrence of VOD [22, 23]. Replacing DNR with GO achieved the same rate of early blast clearance in the bone marrow, CR/CRi after one or two induction cycles, EFS, and OS. Early blast clearance in the bone marrow has been described as an independent prognostic factor for achieving CR and for long-term outcome in earlier AMLCG.
trials [21]. Because of this observation and the fact that the trial was unbiased by crossover or salvage until day 16, we have added this as a primary end point.

Meanwhile, there have been reports on several large multicenter randomized trials testing the impact of GO as part of first-line chemotherapy regimen or as postremission therapy in the treatment of AML [24–27]. The Medical Research Council of UK (MRC) AML15 trial reported by Burnett et al. [24] observed a beneficial effect of a low dose of 3 mg/m² of GO on survival of younger patients with AML, which was largely confined to the good cytogenetic risk group. Due to the limited number of patients in our trial, we have neither prespecified nor carried out extensive comparative subgroup analysis on survival according to risk factors. Other trials incorporating GO into first-line chemotherapy or postremission treatment did not show a beneficial effect of GO or are not yet published.
Recently, the MRC reported data showing that the addition of GO to low-dose ara-C improves remission rates but not survival in older patients not eligible for intensive chemotherapy [28]. Within the published literature, dosing and scheduling of GO is reported with considerable variability. In this study, we had selected a dose and schedule of GO in combination with standard-dose ara-C that was reported as being tolerable and active in a cohort of nine AML patients including patients with relapsed or refractory disease [29]. The induction death rate observed in the 7+GO group was higher than in the 7+3 group but comparable with the death rate of 18% observed in a larger multicenter trial using induction therapy protocols without GO [30].

Currently, the most widely accepted standard of care for induction therapy of elderly patients with newly diagnosed AML and fit for chemotherapy is the ara-C- and DNR-based regimen (7+3) as reported here. The dose of 60 mg/m² DNR was not directly compared, however, with higher doses such as 90 mg/m² [8]. Despite all limitations of study size, our data suggest that in cases of contraindications for nontargeted anthracyclines due to relevant cardiac comorbidities, GO represents an alternative for treatment of elderly AML patients without compromising the potential curability of the disease. Possible occurrence of VOD, however, should be taken into account, and prophylaxis with defibrotide should be given. On the other hand, in this study using a targeted cytotoxic drug as part of induction combination chemotherapy, no primary or secondary end point showed significant superiority of the GO regimen and the trend of a better remission duration was counteracted by higher toxicity. Thus, conduction of larger trials testing the impact of this dose and schedule of GO during first-line treatment of AML in elderly patients cannot be recommended. The strategy of Study Alliance Leukemia (SAL) for the time being will continue to be first-line testing of new drugs targeted to molecules or pathways of importance in the development of AML in a randomized phase II setting for these AML patients with poor prognosis.

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**disclosure**

WEB has served on advisory boards of Wyeth and has obtained honoraria from Wyeth for giving talks in scientific and educational meetings. MK is an employee of Wyeth/Pfizer Germany. All remaining authors declare no conflicts of interest.

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