Low-dose Gemtuzumab-Ozogamicin as post-consolidation therapy in elderly patients with acute myeloid leukaemia: a pilot study

The incidence of acute myeloid leukemia (AML) increases with advancing age, and in older patients the chance of cure has not substantially improved recently. In the elderly the incidence of secondary AML is high, and is often associated with both high-risk cytogenetic abnormalities and expression of the multidrug resistance protein (MDR1) and p-glycoprotein (p-gp), both of which are associated with poor outcomes (Appelbaum *et al*, 2006).

Gemtuzumab-Ozogamicin (GO) is a humanized anti-CD33 monoclonal antibody conjugated to Calicheamicin that is rapidly internalized after binding to CD33. GO seems to be more selective than conventional chemotherapy, as CD33 is expressed on AML cells but not in normal haematopoietic stem cells (SCs) or in non-haematopoietic tissues (Sievers *et al*, 2001). In a series of phase II studies including 142 patients with AML in first relapse, GO monotherapy was associated with a 30% overall complete remission (CR) rate, including a 26% rate in patients over 60 years of age (Sievers *et al*, 2001; Larson *et al*, 2002). These results led to US Food and Drug Administration approval of GO for the treatment of patients over 60 years with relapsed AML (Bross *et al*, 2001). As a consequence of these results, there is interest in extending the use of GO to a frontline treatment for AML in combination with conventional chemotherapy.

Little is known about the usefulness of GO as consolidation and/or maintenance therapy, and no data on the topic have been published to date. In particular, there are no data concerning the safety and efficacy of GO in the setting of post-consolidation therapy in AML patients except for a short report concerning the effects after autologous stem cell transplantation (ASCT) (Cascavilla *et al*, 2008). GO monotherapy has typically been administered as a 2-h infusion at a dose of 9 mg/m^2 on days 1 and 15 of treatment, but the administration of fractionated doses has recently been reported to have a better safety profile (Taksin *et al*, 2007).

We evaluated the efficacy of low-dose GO as late consolidation therapy after CR in a subset of fit elderly patients who were enrolled in a prospective study. From June 1999 to December 2007, 125 patients of 60 years of age or older with morphologically-confirmed AML and non-acute promyelocytic leukaemia were observed in our institution. The preliminary results from 42 patients were reported in 2007 (Olivieri *et al*, 2007). Fit patients, selected according to previously published inclusion criteria (Olivieri *et al*, 2007), were treated with intensive chemotherapy, followed by SC mobilization and ASCT (Olivieri *et al*, 2007). Patients who successfully mobilized SCs underwent ASCT, while poor mobilisers received a further consolidation including standard chemotherapy or investigational immunotherapy with GO.

Among the initial 125 patients, 79 fulfilled the inclusion criteria; of those, 56 (72·1%) achieved CR, and 52 received the first intensive consolidation course followed by G-CSF to collect SC for ASCT. In cases of mobilisation failure, patients were allowed to chose between an experimental approach

Table I. Clinical and biological characteristics of the three groups of patients receiving consolidation with GO (A), ASCT (B), Chemotherapy (CHT) (C) and Allogeneic Transplantation (D).

	A (%)	B (%)	C (%)	D (%)	*P*
Gender					
Male	8 (62)	8 (42·1)	3 (50)	3 (60)	N.S.
Female	5 (38)	11 (57·9)	3 (50)	2 (40)	
Age (years)					
Median = 70 (range, 61–76)					
≤70	7 (54)	10 (52·6)	5 (83·3)	4 (80)	N.S.
>70	6 (46)	9 (47·4)	1 (16·7)	1 (20)	
FAB subtype					
M0	0	5 (26·5)	0	0	N.S.
M1	3 (23)	4 (21)	2 (33·3)	2 (40)	
M2	3 (23)	8 (42)	4 (66·7)	2 (40)	
M4	3 (23)	2 (10·5)	0	1 (20)	
M5	3 (23)	0	0	0	
M6	1 (8)	0	0	0	
M7	0	0	0	0	
Leucocytosis (×10^9/l)					
WBC <10	8 (61·5)	9 (47·4)	4 (66·7)	4 (80)	N.S.
WBC 10–50	5 (38·5)	6 (31·6)	1 (16·7)	1 (20)	
WBC >50	0	4 (21)	1 (16·7)	0	
Karyotype					
Poor	2 (15·4)	7(36·8)	1 (16·7)	4 (80)	N.S.
Intermediate	6 (46·2)	8 (42·1)	4 (66·7)	0	
Favourable	2 (15·4)	0	1 (16·7)	1 (20)	
NE	3 (15·4)	4 (21·1)	0	0	
Secondary disease*					
Yes	3 (23)	8 (42)	2 (33·3)	1 (20)	N.S.
No	10 (77)	11 (58)	4 (66·7)	4 (80)	

FAB, French-American-British classification; NE, not evaluated; WBC, white blood cell.

*To chemotherapy or Myelodysplastic Syndrome.

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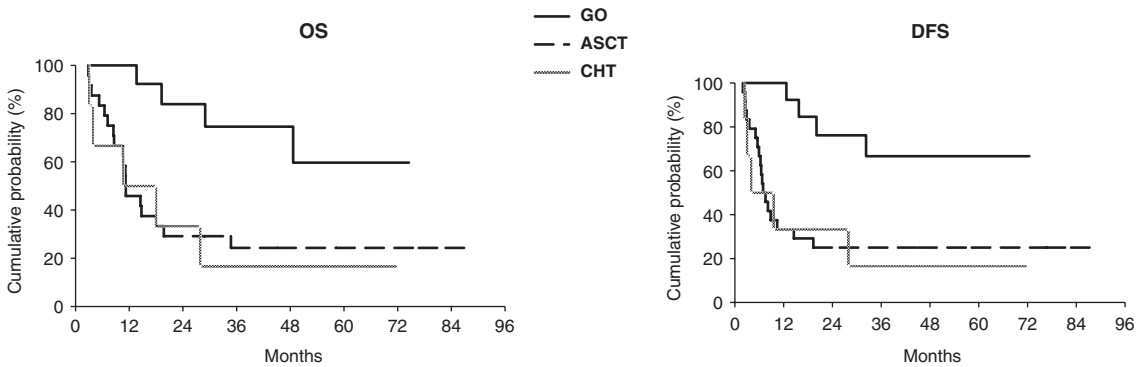

Fig 1. Comparison of the outcome (OS and DFS) of patients receiving late consolidation with Gemtuzumab-Ozogamicin (GO), autologous stem cell transplantation (ASCT) or chemotherapy (CHT) (log rank test).

including low-dose GO or a further conventional consolidation course. GO was administered on a compassionate basis, and the costs were charged to our department. Among the 52 patients who received intensive consolidation, two died and seven relapsed; thus, 43 patients were evaluable for post-remission treatment after the SC mobilization attempt. Of those, 19 patients (44%) successfully mobilized SC and received ASCT. Of the 24 that did not mobilise SC, 13 received GO, six patients refused GO and received a second consolidation with chemotherapy, and five patients received reduced intensity conditioning allogeneic transplant from sibling donors.

The current analysis did not include all patients receiving allogeneic transplant because of the poor prognosis of the disease. The disease characteristics of the remaining patients were equally distributed in the three groups, and the data are shown in Table I.

All the patients received GO at a dose of 3 mg/m^2 three times monthly on an outpatient basis and received common antimicrobial prophylaxis. No patients needed hospitalisation for infections or other major toxicities; the median duration of neutropenia (PMN $<0{\cdot}5 \times 10^9$/l) after GO was 12 d (range 0–33 d). The main toxicities (World Health Organization grade III–IV) were myelosuppression ($n = 9$), hypertransaminasaemia ($n = 1$) and anaphylaxis ($n = 3$); no major unexpected adverse events were observed. With a median follow up of 58 months (range 19–89), a total of 15 patients were alive and in CR: five received ASCT (median follow-up 77 months, range 45-89), nine received GO (median follow-up 38 months, range: 19–75 months), and one, who received chemotherapy, has been followed for 72 months. Two patients receiving GO relapsed and eventually died after 13 and 19 months from CR after the first consolidation. Two more patients relapsed after 15 and 32 months after a second CR after salvage chemotherapy, followed by three doses of GO 3 mg/m^2 administered as consolidation therapy.

In conclusion, nine of the 13 patients who received GO as late consolidation therapy were alive and in continuous CR (including two patients with secondary AML and two with a complex karyotype). The Landmark survival analysis showed better overall survival (OS) and disease-free survival (DFS) ($P = 0{\cdot}017$ and $0{\cdot}01$ respectively) in the 13 patients that received GO (5-year OS, 60%; 5-year DFS, 67%) compared with patients that received either ASCT (5-year OS and DFS: 26%) or chemotherapy (5-year OS and DFS: 17%) (Fig 1). Our preliminary data support a potential role for low-dose GO in consolidation therapy in elderly patients with AML who are able to achieve CR after intensive induction. Late consolidation with low-dose GO seems to be safe and easily manageable; the myelosuppression was relevant, but generally short. All patients received the 3 GO infusions on an outpatient basis without further readmissions and without fatal events.

These preliminary data encourage the use of low-dose GO as late consolidation therapy to eliminate the minimal residual disease (MRD) in older patients with AML. Larger studies are needed for confirmation, possibly including monitoring of MRD during treatment. It also remains to be established if SC collection failure after CR represents an independent favourable prognostic factor in AML patients, as suggested by some retrospective data (Keating *et al*, 2003).

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