ONKOLOGIE

Review Article · Übersichtsarbeit

Onkologie 2007;30:657–662
DOI: 10.1159/000109956

Published online: November 20, 2007

Gemtuzumab Ozogamicin (Mylotarg) for the Treatment of Acute Myeloid Leukemia – Ongoing Trials

Beate Gleissner[a] Richard Schlenk[b] Martin Bornhäuser[c] Wolfgang E. Berdel[d]

[a] Department of Medicine I, University Hospital Saarland, Homburg,
[b] Department of Medicine III, University Ulm,
[c] Department of Medicine I, Technical University Dresden,
[d] Department of Medicine A, University Hospital Münster, Germany

Key Words
Acute myeloid leukemia · Gemtuzumab ozogamicin

Summary
The value of the combination of gemtuzumab ozogamicin (GO) and chemotherapy for the treatment of acute myeloid leukemia (AML) is currently analyzed within clinical trials. GO (6 mg/m^2) and standard-dose cytarabine (100 mg/m^2) is evaluated for the treatment of newly diagnosed AML in elderly patients in the SAL phase II trial. Preliminary results of the MRC AML15 trial support the application of GO 3 mg/m^2 with standard- and high-dose cytarabine and anthracyclines for the treatment of de novo AML. Within this trial the addition of GO seems especially of value for favorable and intermediate cytogenetic risk groups. The combination of GO (3 mg/m^2) and high-dose cytarabine (3 g/m^2) is safe and more effective for the treatment of refractory AML than previous combinations from the AMLSG study group. First results prove the possibility of allogeneic stem cell transplantation after GO therapy. Initial data of a phase II trial document the safety and efficacy profile of GO within a reduced-intensity conditioning protocol applying fludarabine and total body irradiation.

Schlüsselwörter
Akute myeloische Leukämie · Gemtuzumab Ozogamicin

Zusammenfassung
Der Stellenwert von Gemtuzumab Ozogamicin (GO) in der Kombination mit Chemotherapie für die Behandlung der akuten myeloischen Leukämie (AML) wird derzeit auch in Europa untersucht. Der Einsatz von GO (6 mg/m^2) in Kombination mit Cytarabin (100 mg/m^2) bei der Primärbehandlung älterer Patienten mit AML wird in der SAL-Phase-II-Studie geprüft. Das in der MRC-AML15-Studie nachgewiesene verbesserte krankheitsfreie Überleben belegt den Stellenwert von GO (3 mg/m^2) in Kombination mit Standard- und hoch dosiertem Cytarabin und einem Anthrazyklin für die Induktion und Konsolidierung bei neu diagnostizierter AML. Insbesondere Patienten mit einem günstigen und intermediären zytogenetischen Risikoprofil scheinen von der Gabe von GO zu profitieren. In der Behandlung von AML-Rezidiven oder refraktärer Erkrankung erwies sich GO (3 mg/m^2) als sicher mit hoch dosiertem Cytarabin (3 g/m^2) kombinierbar und war in der Wirksamkeit historischen Vergleichskollektiven der AMLSG-Studiengruppe überlegen. Erste Ergebnisse dokumentieren die Möglichkeit einer allogenen Stammzelltransplantation nach GO-Therapie. Erste Daten einer laufenden Studie belegen auch die Einsatzmöglichkeit und das Sicherheitsprofil von GO als Bestandteil einer Konditionierungstherapie von reduzierter Intensität mit Fludarabin und Ganzkörperbestrahlung.

KARGER

Fax +49 761 4 52 07 14
E-mail Information@Karger.de
www.karger.com

Accessible online at:
www.karger.com/onk

PD Dr. med. Beate Gleissner
Universitätsklinikum des Saarlandes
Klinik für Innere Medizin I
Kirrberger Straße, 66421 Homburg, Germany
Tel. +49 6841 16 23-083, Fax -101
E-mail beate.gleissner@uniklinikum-saarland.de

Introduction

Acute myeloid leukemia (AML) is the most frequent leukemia in adults with an incidence of 3.7 in 100,000. Induction therapy with cytarabine (Ara-C) and an anthracycline achieves a complete remission (CR) in 60–80% of the patients [1–3]. However, recurrence occurs in the majority of the patients (50–80%). Salvage therapy is not standardized, and only a median of 25% of patients enter a second CR lasting in most cases 6–8 months [4–7]. 40–50% of the AML patients in 2nd CR achieve a long-term survival after HLA-matched stem cell transplantation (SCT) [8, 9]. However, not every patient qualifies for this treatment approach [10].

After many attempts to improve results with conventional combination chemotherapy, biological agents offer the possibility of an increased response rate [11]. Such therapeutic options include gemtuzumab ozogamicin (GO), which is a humanized monoclonal murine Ig4 antibody (hP67.6) targeting the CD33 antigen. A bifunctional linker conjugates hP67.6 with the antibiotic calicheamicin, which is 1,000 times more cytotoxic than doxorubin. After internalization of the antigen-antibody complex, the low pH of the endosome induces hydrolysis of the linker. Calicheamicin binds sequence specific to DNA, leading to DNA double-strand breaks and apoptosis. GO is an attractive substance, as the CD33 glycoprotein is expressed on 90% of AML blasts. CD33 is also present on myeloid precursor cells, macrophages, monocytes and dendritic cells, but not on hematopoietic stem cells, which are necessary for hematopoietic repopulation [12–14].

Three multicenter phase II trials for relapsed AML were conducted with 2 doses of GO 9 mg/m^2 within 14 days in 277 patients and achieved 13% CR and 13% CR without complete platelet recovery (CRp) [15, 16]. Clinically relevant toxicity was bone marrow suppression and hepatopathy. GO is approved by the Food and Drug Administration (FDA) under the name Mylotarg for monotherapy of relapsed AML in patients older than 60 years and is currently under review for approval at the European Medicines Agency (EMEA). Trials are ongoing that analyze the toxicity profile and the efficacy of GO with combination chemotherapy.

GO Chemotherapy for Relapsed or Refractory AML – the AMLSG 05-04 Trial

In relapsed and refractory AML several combinations of GO (4–9 mg/m^2) with Ara-C (100 mg/m^2) containing regimens have been reported [17–22]. The AMLSG 05-04 trial combines GO (3 mg/m^2) with all-trans retinoic acid (ATRA, 45 mg/m^2 day 4–6, 15 mg/m^2 day 7–28), mitoxantrone (12 mg/m^2 day 2, 3) and high-dose Ara-C (3 g/m^2 day 1–3) (GO-A-HAM) in patients < 60 years with refractory AML. The study recruited up to now 76 patients (84 patients planned). In an interim analysis, GO-A-HAM had similar treatment-related

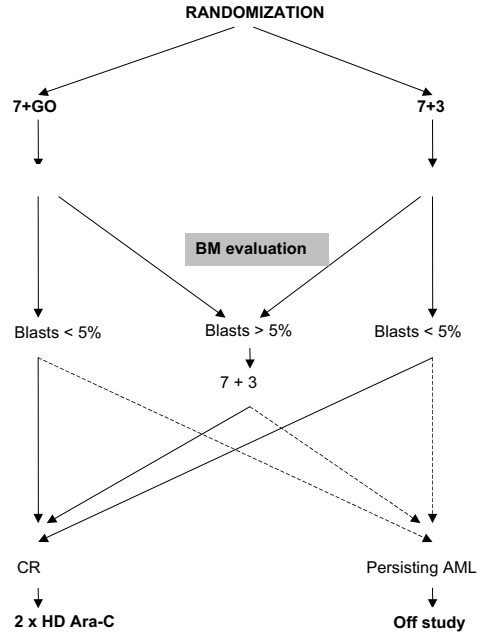

Fig. 1. Design of the SAL phase II trial. The patients are randomized after initial diagnosis to receive either treatment arm A (7+GO: GO 6 mg/m^2, day 1; 4 mg/m^2, day 8 and Ara-C 100 mg/m^2 day 1–7, every 12 h) or Arm B (7+3: dauno-rubicin 45 mg/m^2 day 1–3 and Ara-C 100 mg/m^2 day 1–7 every 12 h). In case of persisting leukemic blasts, patients change to the 7+3 regimen. All patients in complete remission (CR) receive high-dose Ara-C (HD Ara-C) for consolidation treatment. Patients with persisting leukemia go off study. GO = gemtuzumab ozogamicin; Ara-C = cytarabine, BM = bone marrow.

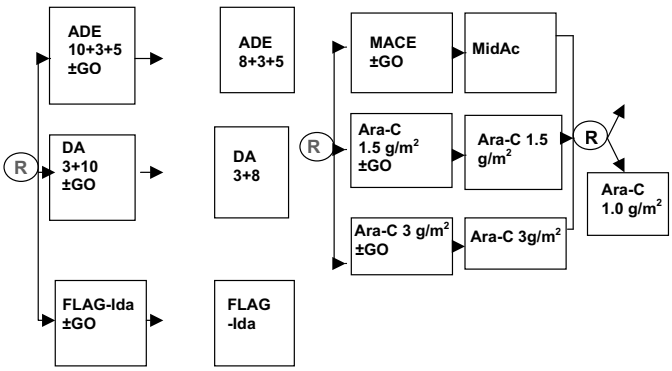

Fig. 2. Design of the MRC AML15 trial. After initial diagnosis patients without an FLT mutation are randomized to a treatment with or without gemtuzumab ozogamicin (GO) and *1. ADE 10+3+5*: Ara-C (cytarabine) 100 mg/m^2 twice daily day 1–10, daunorubicin 50 mg/m^2 day 1, 3, 5, etoposide 100 mg/m^2 day 1–5. The second course *ADE 8+3+5*: Ara-C 100 mg/m^2 twice daily day 1–8, daunorubicin 50 mg/m^2 day 1, 3, 5, etoposide 100 mg/m^2 day 1–5 versus *2. DA 3+10*: daunorubicin 50 mg/m^2 day 1, 3, 5, Ara-C 100 mg/m^2 twice daily day 1–10. The second course of treatment is *DA 3+8*: daunorubicin 50 mg/m^2 day 1, 3, 5, Ara-C 100 mg/m^2 twice daily day 1–8 versus *3. FLAG-Ida*: fludarabine 30 mg/m^2 day 2–6, Ara-C 2 g/m^2, G-CSF day 1–7, idarubicin 8 mg/m^2 day 4, 5, 6. Patients in complete remission (CR) after induction therapy receive one course of consolidation with or without GO and another consolidation course: *1. MACE*: amsacrine 100 mg/m^2 day 1–5, Ara-C 200 mg/m^2 day 1–5, etoposide 100 mg/m^2 day 1–5, followed by MidAc: mitoxantrone 10 mg/m^2 day 1–5 and Ara-C 1 g/m^2 day 1–3 versus *2. Ara-C* 1.5 g/m^2 day 1, 3, 5 versus *3. Ara-C* 3 g/m^2 day 1, 3, 5.

Table 1. Gemtuzumab ozogamicin (GO) in combination with chemotherapy

GO dosage	Chemotherapy	Number of patients treated	Complete remission, %	Nonhematologic toxicity, %[1]	Reference
Relapsed AML					
6 mg/m^2 day 9	Ara-C, G-CSF	14	57	infections 23%	[20]
6 mg/m^2 day 1, 15	IA	14	42	sepsis 71% transaminitis 29%	[17]
9 mg/m^2 day 1	Ara-C, topotecan	17	12	transaminitis 29%	[19]
9 mg/m^2 day 4	MA G-CSF	17	70	hyperbilirubinemia 24% infections 53%	[18]
4.5 mg/m^2 day 1	CSA, fludarabin, Ara-C	32	34	hyperbilirubinemia 44%	[22]
6 mg/m^2 day 1 4 mg/m^2 day 8	Ara-C	9	55	bleeding 33% sepsis 33% transaminitis 33%	[21]
De novo AML					
6 mg/m^2 day 9	Ara-C, G-CSF	12	58		[20]
6 mg/m^2 day 1 4 mg/m^2 day 8	Ara-C	7			[31]
6 mg/m^2 day1	Ara-C	24	36		[31]
3 mg/m^2 day 1	H-DAT	22	91	hepatotoxicity 27%	[28]
6 mg/m^2 day 1	H-DAT	9	89	hepatotoxicity 56%	[28]
3 mg/m^2 day 1	DAT	10	60	hepatotoxicity 40% SOS 20% early deaths 20%	[28]
3 mg/m^2 day 1	DA	8	100	not given	[28]
3 mg/m^2 day 1	FLAG-Ida	15	87	hyperbilirubinemia 20%	[28]
3 mg/m^2 day 1	H-DAT	15	89	hepatotoxicity 33% SOS 33%	[28]
9 mg/m^2 day 1, 8/15	±IL11 15 µg/kg	51	36		[35]
4.5 mg/m^2 day 1	CSA, fludarabine, Ara-C	22		neutropenic fever 23%	[32]
6 mg/m^2 day 1	CSA, fludarabine, Ara-C	59	48	pneumonia 38% FUO 38% hyperbilirubinemia 31%	[32]
6 mg/m^2 day 6	CSA, Ara-C, liposomal daunorubicin	11	18	sepsis 63% hyperbilirubinemia 54% mucositis 27%	[27]
6 mg/m^2 day 4	DA	53	83	mucositis 33%	[33]
6 mg/m^2 day 1/8	Ara-C	21	43	fever 29% chills 41%	[33]
9 mg/m^2 day 1/15		40		infections 40%	[26]
3 mg/m^2 day 1	DAT, DA, or FLAG-Ida followed by MACE	18			[28]
3 mg/m^2 day 1	DAT, DA, or FLAG-Ida, with HD Ara-C	13			[28]
3 mg/m^2 day 1 course 1 and 3	DAT, DA, or FLAG-Ida, with MACE or HD Ara-C	23			[28]
GO 9 mg/m^2 day 1/15 of induction GO 6 mg/m^2 once day 45–60 for consolidation GO 3 mg/m^2 once a month for maintenance		11		FUO 83% cardial 25% pulmonal 25% hypotension 25%	[29, 30]

AML = Acute myeloid leukemia; SOS = sinusoidal obstruction syndrome; FUO = fever of unknown origin; HD Ara-C = high-dose Ara-C; Il 11 = inlerleukin 11; CSA = cyclosporin.
Ara-C, G-CSF: G-CSF 5 µg/kg, day 0–8; Ara-C (cytarabine) 100 mg/m^2 day 4–8.
IA: Idarubicin 12 mg/m^2 day 2–4; Ara-C 1.5 g/m^2 day 2–5.
Ara-C, topotecan: Ara-C 1 g/m^2 day 1–5, topotecan 1.25 mg/m^2 day 1–5.
MA G-CSF: Ara-C 1 g/m^2 /12 h day 1–5, mitoxantrone 12 mg/m^2 day 1–3, G-CSF.
CSA, fludarabin, Ara-C: Fludarabin 15 mg/m^2 day 2–6 (every 12 h), Ara-C 0.5 g/m^2 day 2–6 (every 12 h), CSA 6 mg/kg day 1 + 16 mg/kg continuously iv day 1, 2.
Ara-C: Ara-C 100 mg/m^2 day 1–7 continuously iv.
H-DAT: Daunorubicin day 1, 3, 5; Ara-C 200 mg/m^2 day 1–10; thioguanine 2×/day, day 1–10.
DAT: Daunorubicin day 1, 3, 5; Ara-C 100 mg/m^2 day 1–10; thioguanine 2×/day, day 1–10.
DA: Daunorubicin day 1, 3, 5; Ara-C 100 mg/m^2 day 1–10.
FLAG-Ida: Fludarabine 30 mg/m^2 day 2–6; Ara-C 2 g/m^2, day 2–6; G-CSF, idarubicin 10 mg/m^2 day 4–6.
CSA, Ara-C, liposomal daunorubicin: Ara-C 1 g/m^2 day 1–5 (every 12 h), CSA 6 mg/kg day 6 + 16 mg/kg continuously iv day 6–8, liposomal daunorubicin 75 mg/m^2 day 6–8.
MACE: Amsacrine 100 mg/m^2 day 1–5, Ara-C 200 mg/m^2 day 1–5, etoposide 100 mg/m^2 day 1–5.
[1]Nonhematologic toxicity grade III/IV occurring in more than 20% of the patients.

lethality as A-HAM (ATRA and HAM), S-HAM (sequential high-dose Ara-C) or HAM (high-dose Ara-C). GO-A-HAM induced a CR in 49% of patients, while A-HAM reached a CR in 34%, S-HAM in 23%, and HAM in 24% of patients. 64% of patients with refractory AML responded to the GO-A-HAM regimen (CR and PR). In a retrospective cohort analysis, treatment with ATRA (p = 0.05) and GO (p = 0.05) correlated with a good prognosis. Median survival after GO-A-HAM accounted for 16.2 months (p = 0.002) as compared to 12.5 months after A-HAM or 7.2 months after S-HAM or HAM [23].

Randomized Trials for the Treatment of de novo AML – the SAL Phase II Trial and the MRC AML15 Trial

As the addition of GO to standard chemotherapy 7+3 seemed to be too toxic for elderly patients with AML, the randomized SAL phase II trial compares 7+GO (GO 6 mg/m^2, day 1; 4 mg/m^2, day 8 and Ara-C 100 mg/m^2 day 1–7, every 12 h) with 7+3 (daunorubicin 45 mg/m^2 day 1–3 and Ara-C 100 mg/m^2 day 1–7 every 12 h) for induction treatment of AML in patients > 60 years. The trial design provides consolidation with Ara-C 1 g/m^2 every 12 h day 1, 3, 5. This randomized trial has recruited more than 50 patients so far. The trial is open for participation within the German 'Studien-Allianz Leukämien' (SAL) (fig. 1). The combination of 7+GO may establish a less cardiotoxic primary treatment for newly diagnosed AML in elderly and frail patients, as far as both regimens reach equal toxicity and efficacy.

In patients of all age groups, the MRC AML15 trial analyzed GO (3 mg/m^2) for remission induction and consolidation (GO 6 mg/m^2). This study is based on a 2 × 2 multifactorial design providing different induction and consolidation treatments with and without GO (fig. 2). So far more than 2,000 patients are recruited into the trial. GO was combined in the induction treatment with either ADE (Ara-C, daunorubicin, etoposide; n = 160), DA (daunorubicin, Ara-C; n = 474) or FLAG-Ida (fludarabine, Ara-C, G-CSF, idarubicin; n = 479) in 1,113 patients (median age: 49 years; cytogenetics: favorable 129, intermediate 631, adverse 132) [24]. No increased liver toxicity was observed after GO therapy; similar recovery times were observed for neutrophils (20 days) and platelets (20 days vs 18 days) with and without GO. Similar CR rates were achieved with and without GO (84% with GO vs 86% without GO). Interestingly, at a median follow-up of 16 months in 964 patients, GO led to fewer relapses (37% vs 52% at 3 years, p = 0.01), resulting in a significantly improved disease-free survival (51% vs 40%, p = 0.008) of the patients with de novo AML. No extra liver toxicity was seen in subsequent stem cell transplantations.

GO and Stem Cell Transplantation

Several trials confirmed feasibility of allogeneic SCT in GO-treated patients. After a GO-containing regimen, CR/CRp patients reached a median survival of > 18.3 months (n = 14) with allogeneic SCT, 16.5 months (n = 11) with autologous SCT, 12.2 months with additional chemotherapy (n = 11), and 11.2 months without further treatment (n = 35; p = 0.007) [16]. The German Study Initiative on Leukemias conducted a phase II trial in relapsed AML with reduced-intensity conditioning therapy. So far, results of 19 patients are available that have been treated with GO (GO 6 mg/m^2 day –21 and GO 3 mg/m^2 day –14), fludarabine (30 mg/m^2 day –3 up to day –1), and total body irradiation (TBI; 800 or 200 cGY depending on the relapse-free interval and age), followed by allogeneic SCT in aplasia. After TBI, 75% of patients reached a CR. Seven patients are alive and in CR. With a median follow-up of 21 months no sinusoidal obstruction syndrome (SOS) and delayed liver toxicity was documented. The probability of overall and disease-free survival at 2 years accounted for 51% and 46%, respectively [25].

Conclusion

De novo AML

The toxicity profile allows the application of GO together with chemotherapy (table 1) [20, 26–32]. GO in combination with intensive induction or consolidation therapy was initially analyzed by Kell et al. [28, 33]. GO 3 mg/m^2 proved applicable for induction therapy with daunorubicin and Ara-C or FLAG-Ida as well as MACE (amsacrine, Ara-C, etoposide) or high-dose Ara-C [28]. In the MRC AML15 trial GO (3 mg/m^2) reduced the risk of relapse in de novo AML and improved disease-free survival without additional toxicity. Preliminary data indicate that favorable and intermediate cytogenetic risk groups may particularly benefit from addition of GO. Randomized comparisons of GO and Fms-like tyrosine kinase 3 (FLT-3) inhibitors are ongoing in patients with FLT-3 mutations. Results of the randomized German SAL phase II trial are awaited, that analyzes in elderly patients the substitution of daunorubicin by GO in a setting with standard-dose Ara-C (100 mg/m^2 for 5–7 days).

Relapsed and Refractory AML

Single-agent GO therapy (9 mg/m^2) is approved for the treatment of relapsed AML. Application of GO (3–9 mg/m^2) and chemotherapy (Ara-C 100 mg/m^2–1 g/m^2) achieved CR rates of 12–70% and a median overall survival of 2–11 months in refractory or relapsed AML (table 1) [17–22]. In line with these results are the data of the AMLSG trial that favor the GO-A-HAM (GO 3 mg/m^2) regimen in comparison to other modifications of high-dose Ara-C-containing protocols. Randomized trials are outstanding and data are preliminary.

GO and SCT

The results of Larson et al. confirm feasibility of SCT and GO for the treatment of AML in first relapse [16]. In the context of myeloablative conditioning chemotherapy, SOS developed in 5/27 (19%) patients transplanted prior to GO. SOS occurred in 8/40 (17%) patients transplanted after GO. GO 2 mg/m^2 was applicable with fludarabine/melphalan before allogeneic SCT [34]. The ongoing German trial supports incorporation of GO in a reduced-intensity conditioning regimen with fludarabine and TBI exploiting the aplastic potential of GO within this indication.

References

1 Dillman RO, Davis RB, Green MR, Weiss RB, Gottlieb AJ, Caplan S, Kopel S, Preisler H, McIntyre OR, Schiffer C: A comparative study of two different doses of cytarabine for acute myeloid leukemia: a phase III trial of Cancer and Leukemia Group B. Blood 1991;78:2520–2526.

2 Hann IM, Stevens RF, Goldstone AH, Rees JK, Wheatley K, Gray RG, Burnett AK: Randomized comparison of DAT versus ADE as induction chemotherapy in children and younger adults with acute myeloid leukemia. Results of the Medical Research Council's 10th AML trial (MRC AML 10). Adult and Childhood Leukaemia Working Parties of the Medical Research Council. Blood 1997;89:2311–2318.

3 Buchner T, Berdel WE, Schoch C, Haferlach T, Serve HL, Kienast J, Schnittger S, Kern W, Tchinda J, Reichle A, Lengfelder E, Staib P, Ludwig WD, Aul C, Eimermacher H, Balleisen L, Sauerland MC, Heinecke A, Wormann B, Hiddemann W: Double induction containing either two courses or one course of high-dose cytarabine plus mitoxantrone and postremission therapy by either autologous stem-cell transplantation or by prolonged maintenance for acute myeloid leukemia. J Clin Oncol 2006;24:2480–2489.

4 Craddock C, Tauro S, Moss P, Grimwade D: Biology and management of relapsed acute myeloid leukaemia. Br J Haematol 2005;129:18–34.

5 Smith M, Barnett M, Bassan R, Gatta G, Tondini C, Kern W: Adult acute myeloid leukaemia. Crit Rev Oncol Hematol 2004;50:197–222.

6 Ferrara F, Palmieri S, Mele G: Prognostic factors and therapeutic options for relapsed or refractory acute myeloid leukemia. Haematologica 2004;89:998–1008.

7 Jackson G, Taylor P, Smith GM, Marcus R, Smith A, Chu P, Littlewood TJ, Duncombe A, Hutchinson M, Mehta AB, Johnson SA, Carey P, MacKie MJ, Ganly PS, Turner GE, Deane M, Schey S, Brookes J, Tollerfield SM, Wilson MP: A multicentre, open, non-comparative phase II study of a combination of fludarabine phosphate, cytarabine and granulocyte colony-stimulating factor in relapsed and refractory acute myeloid leukaemia and de novo refractory anaemia with excess of blasts in transformation. Br J Haematol 2001;112:127–137.

8 Aoudjhane M, Labopin M, Gorin NC, Shimoni A, Ruutu T, Kolb HJ, Frassoni F, Boiron JM, Yin JL, Finke J, Shouten H, Blaise D, Falda M, Fauser AA, Esteve J, Polge E, Slavin S, Niederwieser D, Nagler A, Rocha V: Comparative outcome of reduced intensity and myeloablative conditioning regimen in HLA identical sibling allogeneic haematopoietic stem cell transplantation for patients older than 50 years of age with acute myeloblastic leukaemia: a retrospective survey from the Acute Leukemia Working Party (ALWP) of the European Group for Blood and Marrow Transplantation (EBMT). Leukemia 2005;19:2304–2312.

9 Bacigalupo A, Sormani MP, Lamparelli T, Gualandi F, Occhini D, Bregante S, Raiola AM, di Grazia C, Dominietto A, Tedone E, Piaggio G, Podesta M, Bruno B, Oneto R, Lombardi A, Frassoni F, Rolla D, Rollandi G, Viscoli C, Ferro C, Garbarino L, Van Lint MT: Reducing transplant-related mortality after allogeneic hematopoietic stem cell transplantation. Haematologica 2004;89:1238–1247.

10 Forman SJ, Blume KG, Thomas ED (eds): Hematopoietic Cell Transplantation. Boston, Blackwell Science, 2006, pp 823–834.

11 Frankel AE, Sievers EL, Scheinberg DA: Cell surface receptor-targeted therapy of acute myeloid leukemia: a review. Cancer Biother Radiopharm 2000;15:459–476.

12 Bernstein ID, Singer JW, Smith FO, Andrews RG, Flowers DA, Petersens J, Steinmann L, Najfeld V, Savage D, Fruchtman S: Differences in the frequency of normal and clonal precursors of colony-forming cells in chronic myelogenous leukemia and acute myelogenous leukemia. Blood 1992;79:1811–1816.

13 Griffin JD, Linch D, Sabbath K, Larcom P, Schlossman SF: A monoclonal antibody reactive with normal and leukemic human myeloid progenitor cells. Leuk Res 1984;8:521–534.

14 Scheinberg DA, Lovett D, Divgi CR, Graham MC, Berman E, Pentlow K, Feirt N, Finn RD, Clarkson BD, Gee TS: A phase I trial of monoclonal antibody M195 in acute myelogenous leukemia: specific bone marrow targeting and internalization of radionuclide. J Clin Oncol 1991;9:478–490.

15 Sievers EL, Larson RA, Stadtmauer EA, Estey E, Lowenberg B, Dombret H, Karanes C, Theobald M, Bennett JM, Sherman ML, Berger MS, Eten CB, Loken MR, van Dongen JJ, Bernstein ID, Appelbaum FR: Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. J Clin Oncol 2001;19:3244–3254.

16 Larson RA, Sievers EL, Stadtmauer EA, Lowenberg B, Estey EH, Dombret H, Theobald M, Voliotis D, Bennett JM, Richie M, Leopold LH, Berger MS, Sherman ML, Loken MR, van Dongen JJ, Bernstein ID, Appelbaum FR: Final report of the efficacy and safety of gemtuzumab ozogamicin (Mylotarg) in patients with CD33-positive acute myeloid leukemia in first recurrence. Cancer 2005;104:1442–1452.

17 Alvarado Y, Tsimberidou A, Kantarjian H, Cortes J, Garcia-Manero G, Faderl S, Thomas D, Estey E, Giles FJ: Pilot study of Mylotarg, idarubicin and cytarabine combination regimen in patients with primary resistant or relapsed acute myeloid leukemia. Cancer Chemother Pharmacol 2003;51:87–90.

18 Chevallier P, Roland V, Mahe B, Juge-Morineau N, Dubruille V, Guillaume T, Vigouroux S, Moreau P, Milpied N, Garand R, vet-Loiseau H, Harousseau JL: Administration of Mylotarg 4 days after beginning of a chemotherapy including intermediate-dose aracytin and mitoxantrone (MIDAM regimen) produces a high rate of complete hematologic remission in patients with CD33+ primary resistant or relapsed acute myeloid leukemia. Leuk Res 2005;29:1003–1007.

19 Cortes J, Tsimberidou AM, Alvarez R, Thomas D, Beran M, Kantarjian H, Estey E, Giles FJ: Mylotarg combined with topotecan and cytarabine in patients with refractory acute myelogenous leukemia. Cancer Chemother Pharmacol 2002;50:497–500.

20 Fianchi L, Leoni F, Storti S, Rutella S, Gianfaldoni G, Voso MT, Bosi S, Pagano L, Leone G: Gemtuzumab-ozogamicin, citosine arabinoside, G-CSF combination in the treatment of elderly patients with poor prognosis acute myeloid leukemia. A multicentric study. Blood 2005;106:230B.

21 Piccaluga PP, Martinelli G, Rondoni M, Malagola M, Gaitani S, Visani G, Baccarani M: First experience with gemtuzumab ozogamicin plus cytarabine as continuous infusion for elderly acute myeloid leukaemia patients. Leuk Res 2004;28:987–990.

22 Tsimberidou A, Cortes J, Thomas D, Garcia-Manero G, Verstovsek S, Faderl S, Albitar M, Kantarjian H, Estey E, Giles FJ: Gemtuzumab ozogamicin, fludarabine, cytarabine and cyclosporine combination regimen in patients with CD33+ primary resistant or relapsed acute myeloid leukemia. Leuk Res 2003;27:893–897.

23 Schlenk RF, Doehner K, Kerz M, Hartman R, del Valle F, Glasmacher A, Pralle H, Goetze K, Koller E, Gastl G, Mergenthaler HG, Salwender H, Kirchen H, Haase D, Kremers S, Nerl C, Heobald M, Matzdorff AC, Ganser A, Doehner H for the German-Austrian AML Study Group AMLSG: All-trans retinoic acid and gemtuzumab ozogamicin as adjunct to salvage therapy in primary refractory acute myeloid leukemia: results of consecutive phase II studies of the AMLSG. Blood 2006;106:526a.

24 Burnett AK, Kell WJ, Goldstone AH, Milligan DW, Hunter A, Prentice AG, Russellm BG, Gibson B, Willemze R, Hills RK: The addition of gemtuzumab ozogamicin to induction chemotherapy for AML improves disease free survival without extra toxicity. Preliminary analysis of 1115 patients in the MTC AML15 trial. Blood 2006;106:8a.

25 Bornhauser M, Illmer T, Platzbecker U, Ordemann R, Schetelig J, Schaich M, Kiani A, Schuler U, Ehninger G: Gemtuzumab ozogamicin (Mylotarg®) followed by dose-reduced total-body irradiation and fludarabine as conditioning for allogeneic stem cell transplantation in patients with relapsed/refractory CD33+ acute myeloid leukaemia. Bone Marrow Transplant 2006;37:S121.

26 Amadori S, Suciu S, Stasi R, Willemze R, Mandelli F, Selleslag D, Denzlinger C, Muus P, Stauder R, Berneman Z, Pruijt J, Nobile F, Cassibba V, Marie JP, Beeldens F, Baila L, Vignetti M, de Witte T: Gemtuzumab ozogamicin (Mylotarg) as single-agent treatment for frail patients 61 years of age and older with acute myeloid leukemia: final results of AML-15B, a phase 2 study of the European Organisation for Research and Treatment of Cancer and Gruppo Italiano Malattie Ematologiche dell'Adulto Leukemia Groups. Leukemia 2005;19: 1768–1773.
27 Apostolidou E, Cortes J, Tsimberidou A, Estey E, Kantarjian H, Giles FJ: Pilot study of gemtuzumab ozogamicin, liposomal daunorubicin, cytarabine and cyclosporine regimen in patients with refractory acute myelogenous leukemia. Leuk Res 2003; 27:887–891.
28 Kell WJ, Burnett AK, Chopra R, Yin JA, Clark RE, Rohatiner A, Culligan D, Hunter A, Prentice AG, Milligan DW: A feasibility study of simultaneous administration of gemtuzumab ozogamicin with intensive chemotherapy in induction and consolidation in younger patients with acute myeloid leukemia. Blood 2003;102:4277–4283.
29 Nabhan C, Rundhaugen L, Jatoi M, Riley MB, Boehlke L, Peterson LC, Tallman MS: Gemtuzumab ozogamicin (Mylotarg™) is infrequently associated with sinusoidal obstructive syndrome/veno-occlusive disease. Ann Oncol 2004;15:1231–1236.
30 Nabhan C, Rundhaugen LM, Riley MB, Rademaker A, Boehlke L, Jatoi M, Tallman MS: Phase II pilot trial of gemtuzumab ozogamicin (GO) as first line therapy in acute myeloid leukemia patients age 65 or older. Leuk Res 2005;29:53–57.
31 Roboz GJ, Ritchie EK, Schuster MW, Shore T, Curcio TJ, Allen-Bard S, Provenzano JL, Feldman EJ: Gemtuzumab ozogamicin is an acceptable alternative to anthracyclines in combination with standard dose infusional cytarabine as induction therapy for elderly patients with acute myeloid leukemia (AML). Blood 2006;106:528a.
32 Tsimberidou AM, Estey E, Cortes JE, Garcia-Manero G, Faderl S, Verstovsek S, Thomas DA, Ferrajoli A, Keating MJ, O'Brien S, Kantarjian HM, Giles FJ: Mylotarg, fludarabine, cytarabine (ara-C), and cyclosporine (MFAC) regimen as post-remission therapy in acute myelogenous leukemia. Cancer Chemother Pharmacol 2003;52:449–452.
33 De Angelo DJ, Stone RM, Durrant S, Liu D, Baccarani M, Schiffer CA, Amrein P, Sherman ML, Mylotarg Study Group: Gemtuzumab ozogamicin (Mylotarg) in combination induction chemotherapy for the treatment of patients with de novo acute myeloid leukemia: two age-specific phase 2 trials. Blood 2003;102:341a.
34 de Lima M, Giralt S, Caldera Z, McCormick G, Qazilbash M, Anderlini P, Shpall EJ, Hosing C, Donato M, Kornblau S, Khouri I, Martin T, Couriel D, Champlin R: Results of a phase I/II study of gemtuzumab ozogamicin added to fludarabine (F); melphalan (M) and allogeneic hematopoietic stem cell transplantation (HSCT) for relapsed myeloid leukemias. Blood 2006;106:248a.
35 Estey EH, Thall PF, Giles FJ, Wang XM, Cortes JE, Beran M, Pierce SA, Thomas DA, Kantarjian HM: Gemtuzumab ozogamicin with or without interleukin 11 in patients 65 years of age or older with untreated acute myeloid leukemia and high-risk myelodysplastic syndrome: comparison with idarubicin plus continuous-infusion, high-dose cytosine arabinoside. Blood 2002;99:4343–4349.