Gemtuzumab ozogamicin

[haematologica reports]
2005;1(8):18-19

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Treatment outcome for acute myeloid leukemia (AML) has substantially improved over the last decade, especially in patients younger than 60 years of age who can tolerate intensified treatment strategies including hematopoietic stem cell transplantation.[1] On the other hand, there has been little progress in the treatment of older patients where intensive chemotherapy regimens are associated with a lower complete remission (CR) rate, an increased risk of relapse and an inferior overall survival.[2-3] Factors which have been considered important in explaining the adverse effect of age include: 1) reduced ability of older patients to withstand the morbidity associated with chemotherapy-induced marrow hypoplasia; 2) concurrent medical problems; 3) unfavourable biologic profile of the disease as documented by a high proportion of patients presenting with adverse cytogenetics, preexisting myelodysplasia, stem cell and chemoresistant phenotype. Despite years of research and therapeutic improvements, the majority of patients with AML, regardless of age at diagnosis, will eventually die from their disease. Thus, there is a need to identify innovative treatment strategies to improve survival. The availability of antibodies reactive with antigens expressed preferentially by hematopoietic cells has provided investigators with new tools for designing innovative treatment strategies for AML. The CD33 antigen, a 67-kD glycosylated transmembrane protein of unknown function, is expressed on the surface of leukemic blasts in more than 90% of patients with AML.[4] The antigen is also expressed by myelomonocytic precursor cells and to a lesser extent by mature myeloid cells, but not by primitive hematopoietic cells and non-hematopoietic tissues, making it an attractive target for AML therapy. Gemtuzumab ozogamicin (GO) is an immunoconjugate composed of a recombinant humanized murine anti-CD33 antibody linked to the potent antitumor antibiotic calicheamicin, and provides a novel method of drug delivery by using the monoclonal antibody to target the CD33-positive cells.[5] Upon binding to the CD33 antigen, the immunotoxin is internalized into target cells and the calicheamicin is released intracellularly. The released calicheamicin binds to DNA in the minor groove resulting in DNA double strand breaks and cell death.[6] By targeting cells that only express this antigen, GO is able to eliminate the leukemic blasts from the marrow and blood without many of the systemic toxicities, such as mucositis, associated with traditional chemotherapeutic agents. In combined phase II studies of 142 patients with AML in first relapse, GO monotherapy (two doses of 9 mg/m^2 given 14 days apart) was associated with a 30% overall complete remission rate, including a 26% response rate in patients over 60 years of age 7. Although myelosuppression and reversible increases in levels of serum bilirubin and transaminases were commonly observed, severe mucositis and grade 3-4 infections were not. These results led in May 2000 to the US Food and Drug Administration approval of GO for the treatment of patients over 60 years of age with relapsed AML. The results of phase II trials suggest that single agent GO administered to patients with AML in first relapse has an efficacy comparable to that of current salvage chemotherapy regimens. The favourable safety profile supports its use in combination with frontline conventional induction and/or consolidation chemotherapy in patients considered to be eligible for an intensive treatment approach, as well as monotherapy in patients for whom intensive cytotoxic regimens would be considered unsuitable, such as many patients older than 60 years of age. Several large groups are currently evaluating this targeted therapy in combination trials as frontline therapy. The SWOG is conducting a randomized phase 3 trial (S0106) in adults (<56 years of age) with previously untreated AML. Main objectives of this trial are: to compare the CR rates achieved by the addition of GO (6 mg/m^2 on day 4) to standard induction chemotherapy (daunorubicin + cytarabine, "3+7") versus standard induction alone; to compare the disease-free survival of patients

who receive GO (5 mg/m^2×3 monthly doses) as post-consolidation therapy versus no post-consolidation therapy. Accrual is anticipated to be 684 patients and will continue until 342 patients undergo second randomization. The MRC is currently investigating the feasibility of combining GO with intensive chemotherapy in patients younger than 60 years of age (AML 15 study). The study design was based on the results of the AML 12 pilot study, as follows 8: combining GO 3 mg/m^2 with DAT (daunorubicin, cytarabine, thioguanine), DA (daunorubicin, cytarabine), or FLAG-Ida (fludarabine, cytarabine, G-CSF and idarubicin) is feasible, but DAT is associated with liver toxicity; combining GO (6 mg/m^2 or 3 mg/m^2) with two consecutive induction courses is not feasible because of toxicity; thioguanine contributes to liver toxicity; combining GO with induction and consolidation is feasible; the addition of GO to induction chemotherapy produces high CR rates. In AML 15, patients are first randomized to receive either ADE (daunorubicin, cytarabine, etoposide) 10+3+5 followed by ADE 8+3+5, DA 3+10±GO followed by DA 3+8, or FLAG-Ida±GO followed by FLAG-Ida on first and second induction course. During the second randomization, patients receive two courses of consolidation with MACE (amsacrine, cytarabine, etoposide) ± GO followed by mitoxantrone+cytarabine, or cytarabine (1.5 g/m^2) ± GO followed by cytarabine (1.5 g/m^2), or cytarabine (3 g/m^2) ± GO followed by cytarabine (3 g/m^2). Finally, all patients are randomized to receive either one course of cytarabine (1.0 g/m^2) or no further treatment. The ECOG is conducting a phase 2 trial designed to assess daunorubicin dose intensification during induction, and GO (6 mg/m^2) consolidation therapy one month prior to autologous stem cell transplantation. Main objectives of the study are: to compare disease-free survival between the consolidation regimens; to evaluate the effect of GO on *in vivo* purging; to evaluate the safety of GO before autografting. The accrual goal is 747 eligible patients. The EORTC Leukemia Group in collaboration with GIMEMA is currently running two prospective randomized trials for patients older than 61 years of age with untreated AML. AML-17 is a phase 3 study which was designed to address the comparative benefits of GO (6 mg/m^2 on day 1 and 15) combined with sequential standard chemotherapy (MICE regimen) versus standard chemotherapy alone for induction of remission, followed by two rounds of mini-ICE ± GO (3 mg/m^2 on day 0) for consolidation. The study design was based on the results of the AML-15A pilot study (57 patients), as follows 9: combining GO (9 mg/m^2 for two doses, 14 days apart) with sequential MICE is feasible in 67% of patients; the rate of initial response (CR+CRp) to single agent GO is substantial (35%), and the overall complete remission rate to the entire induction sequence is in the 54% range; other than myelosuppression, grade 3-4 hepatotoxicity is the main adverse events including five cases of VOD (9%). In the parallel AML-15B pilot study, 40 patients considered to be ineligible for standard chemotherapy (age >75 years, or performance status WHO grade 2) received GO at the FDA-approved dose-schedule (9 mg/m^2 on day 1 and 15) as frontline induction therapy, and those entering CR/CRp received two additional monthly doses of GO as consolidation. The overall response (CR+CRp) rate was 17.5%. The rate of response in patients 61-75 years old was 33% (6/18), and 5% (1/22) in patients older than 75 years. Profound myelosuppression was common, and overall induction mortality was 17.5% (32% in patients >75 years old). Ten percent of patients experienced grade 3-4 liver toxicity, including one case of VOD. These results have triggered the design of the AML-19 trial, a phase 2-3 study that will target AML patients considered to be unsuitable for standard chemotherapy (age >75 years; age 61-75 years with a WHO performance status >2) or unwilling to receive it. In the phase 2 portion of the trial, a reduced total dose of GO (9 mg/m^2) is administered over a short time interval according to two different fractionated schedules (regimen A: 6 mg/m^2 on day 1 and 3 mg/m^2 on day 8; regimen B: 3 mg/m^2 on days 1, 3 and 5). The most successful investigational regimen from phase 2 will be carried into phase 3 and compared to standard supportive care.

References

1. Zittoun R, Mandelli F, Willemze R, et al. Autologous and allogeneic bone marrow transplantation versus intensive chemotherapy in acute myelogenous leukemia. N Engl J Med. 1995; 332:217-23.
2. Stasi R, Venditti A. Del Poeta G, et al. Intensive treatment of patients age 60 years and older with de novo acute myeloid leukemia. Analysis of prognostic factors. Cancer, 1996; 77: 2476-88.
3. Hiddemann W, Kern W, Schoch C, et al. Management of acute myeloid leukemia in elderly patients. J Clin Oncol 1999;17: 3569-76.
4. Dinndorf PA, Andrews RG, Benjamin D, et al. Expression of normal myeloid-associated antigens by acute leukemia cells. Blood 1986;67:1048-53.
5. Hamann PR, Hinman LM, Hollander I, et al. Gemtuzumab ozogamicin, a potent and selective anti-CD33 antibody-calicheamicin conjugate for treatment of acute myeloid leukemia. Bioconjugate Chem. 2002;13: 47-58.
6. Zein N, Sinha A, McGahren W, Ellestad G. Calicheamycin Á1: an antitumor antibiotic that cleaves double-stranded DNA site specifically. Science 1988;240: 1198-1201.
7. Sievers EL, Larson RA, Stadtmauer EA, et al. Efficacy and safety of gemtuzumab ozogamicin in patients with CD33-positive acute myeloid leukemia in first relapse. J. Clin. Oncol. 2001;19: 3244-54.
8. Kell WJ, Burnett AK, Chopra R, et al. 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: 4277-83.
9. Amadori S, Suciu S, Willemze R, et al. Sequential administration of gemtuzumab ozogamicin and conventional chemotherapy as first line therapy in elderly patients with acute myeloid leukemia: a phase II study (AML-15) of the EORTC and GIMEMA leukemia groups. Haematologica 2004;89: 950-6.