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New agents for the treatment of acute myeloid leukemia: gemtuzumab ozogamicin

The CD33 antigen is a 67-kD sialic acid-dependent adhesion protein that is specific for myeloid cells. CD33 is expressed on approximately 90% of AML cases, as defined by the presence of the antigen on greater than 20% of the leukemic blasts, but not on normal CD34⁺ pluripotent hematopoietic stem cells or non-hematopoietic tissues.¹

Gemtuzumab ozogamicin consists of a semisynthetic derivative of calicheamicin, a potent cytotoxic antibiotic, linked to a humanized IgG4 anti-CD33 monoclonal antibody (hP67.6). The hP67.6 antibody is non-cytotoxic by itself.² *In vitro* data indicate that when GO binds the CD33 antigen, the complex is rapidly internalized.^{3,4} Upon internalization, the calicheamicin derivative is released inside the lysosomes of the myeloid cell by acid hydrolysis. The released calicheamicin derivative binds to DNA in the minor groove resulting in DNA double strand breaks and cell death by apoptosis.

GO monotherapy in patients with AML in first relapse was first investigated in three pivotal phase II trials multicenter trials in North America and Europe (0903B1-201-US/CA, 0903B1 202 EU, 0903B1-203-US/EU) with a total of 277 patients.⁵ Patients with a median age of 61 years received GO 9 mg/m² as a 2-hour intra-

venous infusion in 2 doses separated by 2 weeks. Using the 1988 criteria of the the National Cancer Institute (protocol-defined criteria)⁶, 13% of patients achieved a CR and 13% a CR with incomplete platelet recovery (CRp). GO was found to be equally effective in patients 60 years old or over (overall response rate 26%) and in younger patients (overall response rate 34%). Furthermore, the adverse effects were similar in the two age groups. The median overall survival was 4.8 months (5.3 months and 4.5 months for patients younger than 60 yrs and age 60 yrs and older, respectively). The early death rate (death within 28 days) was 16%. Median survival for responders (CR+CRp) was 12.5 months. Remission duration ranged between 4.5 (CRp patients) and 6.4 months (CR patients). A significant difference in remission duration was observed between patients younger than 60 years and patients age 60 years and older ($p=0.008$). This was possibly affected by postremission treatment options, especially hematopoietic stem cell transplantation (HSCT).

Additional reports on the effectiveness of single agent GO in unselected older patients with newly diagnosed AML have been rather disappointing, with overall response rates (CR/CRp) seldom

exceeding 25-30%.⁷ A number of phase II studies in relapsed/refractory cases and in patients with previously untreated AML have also assessed the feasibility of treatment protocols integrating GO and chemotherapy, and have been reviewed recently.⁷ The results of these trials are quite heterogeneous, reflecting not only the variable activity of the regimens used, but also the different characteristics of the patient populations.

Several cooperative groups have published the results of their pilot trials in patients with untreated AML, and have used these results to design prospective randomized trials. The EORTC/GIMEMA group investigated the effects of standard intensive chemotherapy, with or without GO administered frontline, as induction and consolidation therapy in patients aged 61-75 years.⁸ The overall response rate to the entire induction sequence was 54.4% (31/57), with CR in 35.1% and CRp in 19.3%. An initial response to GO was documented in 20 patients (35.1%), with CR in 22.8% and CRp in 12.3%. This sequential regimen is being investigated in a phase III trial (AML-17). A second trial (AML-19) includes GO monotherapy versus standard supportive care in patients with untreated AML older than 75 years who are not candidates for intensive chemotherapy.

The Medical Research Council (MRC) evaluated the feasibility of combining lower doses of GO (3 mg/m²) with three different intensive chemotherapy regimens as first-line treatment in 72 AML patients aged 17-59 years.⁹ They obtained CR rates ranging from 86-91%, with a higher frequency of Grade 4 liver toxicity and sinusoidal obstructive syndrome in thioguanine containing schedules. The experience of this pilot trial was used to design the MRC AML15 study, which randomly assigned patients <60 years of age to receive induction chemotherapy ± GO/consolidation ± GO. A preliminary analysis on 1115 patients indicated

that the use of GO (3 mg/m² on day 1) results in a significant reduction in relapse risk (37% vs. 52% at 3 years, $p=0.01$) and improvement in DFS (51% vs. 40% at 3 years, $p=0.008$).¹⁰ A subset analysis showed that GO is beneficial for patients with favorable or intermediate-risk cytogenetics but not for those with adverse cytogenetics. Subsequent follow-up has even shown a significant overall survival benefit in the favorable and intermediate groups.¹¹ Interestingly, in this trial P-glycoprotein expression, which is known to be inversely related to calicheamicin activity *in vitro*, appeared to have little effect on outcome. Also, the risk of hepatotoxicity in patients who subsequently went on to transplantation did not appear increased. Other phase III studies that incorporate GO as part of standard induction chemotherapy in newly diagnosed patients with AML are ongoing (see <http://www.cancer.gov/clinicaltrials/> for additional details).

Acute promyelocytic leukemia (APL) is an ideal model to test the efficacy of GO because of the high and homogeneous expression of the CD33 antigen and lack of, or very low levels of, multidrug resistance mechanisms. In fact, GO monotherapy is highly active not only in patients with APL at molecular relapse,¹² but even in the setting of overt or advanced disease.¹³⁻¹⁵

The cumulative experience with gemtuzumab ozogamicin suggests it is relatively well tolerated in patients of all ages receiving treatment for AML in first relapse. The safety profile does not differ significantly between patients <60 years and patients ≥60 years. However, the immunoconjugate therapy appears particularly toxic in patients older than 75 years, for whom a dose reduction has been proposed.¹⁶ The administration of fractionated doses of GO (3 mg/m² on days 1, 4 and 7 for one course) demonstrated an excellent efficacy/safety profile, and may represent a valuable alternative for frailer patients.¹⁷ The main safe-

ty issues consist of severe myelosuppression, hepatotoxicity including VOD/SOS and infusion related events. Caution should be exercised when using GO in routine clinical practice, particularly if administered with other hepatotoxic agents, in those with pre-existing hepatic pathology, or within 3 months of a SCT procedure. In general, prior exposure to GO significantly increases the risk of hepatic VOD in patients undergoing myeloablative allogeneic SCT, but this risk decreases if at least 3 months have elapsed since the last dose of GO. The use of doses ≤ 6 mg/m² appears to be equally effective than the FDA-licensed dose of 9 mg/m² and is characterized by the absence of significant side effects, particularly VOD.

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