Low dose gemtuzumab ozogamicin for relapsed acute myeloid leukaemia in elderly

Haematologica 2007; 88:(12)e165-e166

Introduction. Acute myeloid leukemia (AML) in the elderly presents with peculiar characteristics, and current conventional approaches achieve only poor results, especially in relapsed patients.[1] In particular, intensified regimens do not offer advantages in terms of clinical response, and even cause significant toxicity.[1,2,3] Thus, alternative strategies able to combine efficacy and a low profile of toxicity, and in particular monoclonal antibodies, are under investigation.[4] Gemtuzumab ozogamicin (formerly CMA-676; Wyeth Laboratories, Philadelphia, PA, USA), a humanized anti-CD33 monoclonal antibody conjugated to calicheamicin, is effective in relapsed AML patients, also in the elderly.[5,6,7,8] Nevertheless, conventional doses are characterized by not irrelevant toxicity, especially in heavily pre-treated patients.[8,9,10] We treated an AML patient not table to receive standard doses with low dose GO, in order to limit the possible occurrence of adverse events.

Case Report. A 56-years old man was diagnosed with acute myeloid leukemia (M2 FAB-subtype; normal karyotype) in 1996. He received 2 courses of mini-ICE chemotherapy (idarubicin 10 mg/m^2/day for 3 days, etoposide 100 mg/m^2/day for 5 days, and cytarabine 100 mg/m^2/day in continuous i.v. perfusion for 5 days), achieving a complete remission. He was then submitted to autologous bone marrow transplantation. Subsequently, he received low-dose sub-cutaneous cytarabine (20 mg for 7 days, every 45 days), as maintenance therapy. This therapy was retained until the relapse occurred, in October 2002, because, despite a bone marrow CR, as assessed at morphologic examination, a minimal residual amount of blasts, around 3-5% was always present. At the time of relapse, the bone marrow aspirate was normo-hypocellular with 65% of blasts. We did not administer any cytotoxic treatment, considering the poor clinical condition and the good peripheral blood counts (WBC=4.7x10^9/L, 56% ANC and 0% blasts, Hb=12.9 g/dL, PLT=266x10^9/L). Five months later, due to the worsening blood counts, especially concerning the ANC number (WBC=2.1x10^9/L - with 12% ANC, and 0% blasts - Hb=10.6 g/dL, and PLT=198x10^9/L), we decided to treat the patient with low dose gemtuzumab ozogamicin (GO) (1.5 mg/m^2). At this time the bone marrow aspirate was normo-hypocellular with 90% of blasts. The peripheral blood cell count nadir was reached 5 days after therapy (ANC=0.2x10^9/L, PLT=100x10^9/L, Hb=10.5 g/dL). Thirteen days after the GO administration, ANC had recovered up to 1.0x10^9/L. The PLT count was never lower than 100x10^9/L. No transfusions were required. During neutropenia, the patient developed a pulmonary aspergillosis, treated with fungizone, 50 mg/m^2 for 14 days. No laboratory abnormalities were observed. The post-treatment bone marrow aspirate was normo-hypocellular, with no blasts. Peripheral blood counts were: WBC=10.7x10^9/L, 72% ANC and 0% blasts, Hb=10.4 g/dL, PLT=255x10^9/L. The CR was maintained for 6 months, and then the patient relapsed. At present, the bone marrow aspirate is normocellular, with 70% of myeloid blasts, and the peripheral blood counts are: Hb 11 g/dL, WBC 3.9x10^9/L (50% ANC, and 0% blasts), PLT 162 x109/L, without transfusions. Due to the high risk of fungal infection, no further chemotherapy has been proposed.

Discussion and Conclusion. GO is currently administered at a dose of 9 mg/m^2 as a single agent, and 4-6 mg/m^2 when given in combination with other chemotherapy.[8,11] The pharmacokinetics of GO is not erratic,[12] and doses lower than 4 mg/m^2 seem not able to induce complete saturation of CD33 in bone marrow and peripheral blood.[5,13] Thus, low doses are not used in the treatment of active leukemia, but have been proposed only as maintenance therapy. In the present case we documented the ability of very low doses of GO (1.5 mg/m^2) to induce CR in a relapsed elderly AML patient, a phenomenon not previously reported. Notably, the treatment-related toxicity was very limited. In fact, the only adverse event was a fungal infection, most likely related to neutropenia, a condition already present before GO administration. It should be considered that although an elderly relapsed AML patient always has very little chance of achieving a new remission, in this case the quite long first CR duration (approximately 6 years) can be considered as a relatively good prognostic feature. Nevertheless, in our opinion, our observation is noteworthy. In fact, this schedule could be proposed to patients not suitable for standard doses. Secondly, since GO in association with conventional chemotherapy seems quite toxic,[11] lower doses of GO may be suggested for combination regimens. Nevertheless, larger studies are warranted in order to confirm our findings, and eventually assess the role of low-dose GO in AML therapy.

P.P. Piccaluga,[1] G. Martinelli,[1] M. Rondoni,[1] M. Malagola,[1] S. Ronconi,[2] G. Visani,[3] M. Baccarani[1]
[1]Institute of Haematology and Medical Oncology "L. and A. Seràgnoli", S. Orsola-Malpighi Hospital, University of Bologna, Italy
Current address: Institute for Cancer Genetics, Columbia University, New York, NY, USA
[2]Oncology Division, Pierantoni Hospital, Forlì, Italy
[3]Department of Haematology, S. Salvatore Hospital, Pesaro, Italy
Correspondence: Pier Paolo Piccaluga, MD. Institute Institute for Cancer Genetics, Columbia University, 1150 St Nicholas Avenue, Room307, New York, NY, USA
Tel: 001-212-851-5270 - Fax: 001-212-851-5256
Acknowledgments: supported in part by AIL (Bologna and Pesaro) ONLUS, AIRC, COFIN 2001-2002 (M. Baccarani and S. Tura) grants. PPP was also supported by Rotary International-The Rotary Foundation, Cristina Bassi Association and Centro Interdipartimentale di Ricerche sul Cancro "Giorgio Prodi" (CIRC)
Key words: gemtuzumab ozogamicin, antibody-targeted chemother-

apy, acute myeloid leukemia, elderly

References

1. Rowe JM. Treatment of acute myelogenous leukemia in older adults. Leukemia, 2000;14:480-7.
2. Ferrara F, Morabito F, Latagliata R, Martino B, Annunziata M, Oliva E, et al. Aggressive salvage treatment is not appropriate for the majority of elderly patients with acute myeloid leukemia relapsed from first complete remission. Haematologica, 2001;86:814-20.
3. Schaich M, Illmer T, Aulitzky W, Bodenstein H, Clemens M, Neubauer A, et al. Intensified double induction therapy with high dose mitoxantrone, etoposide, m-amsacrine and high dose ara-C for elderly acute myeloid leukemia patients aged 61-65 years. Haematologica, 2002;87:808-15.
4. Tomblyn MR, Tallman MS. New developments in antibody therapy for acute myeloid leukemia. Semin Oncol, 2003;30:502-8.
5. Sievers EL, Appelbaum FR, Spielberger RT, Forman SJ, Flowers D, Smith FO, et al. Selective ablation of acute myeloid leukemia using antibody-targeted chemotherapy: a phase I study of an anti-CD33 calicheamicin immunoconjugate. Blood, 1999;93:3678-84.
6. Bross PF, Beitz J, Chen G, Chen XH, Duffy E, Kieffer L, et al. Approval summary: gemtuzumab ozogamicin in relapsed acute myeloid leukemia. Clin Cancer Res. 2001;7:1490-6.
7. Hermida G, Manjon R, Rodriguez-Salazar I, Richard C. Treatment of a secondary myelodysplastic syndrome after allogenic bone marrow transplantation using Mylotarg. Haematologica, 2002;87:ECR14.
8. Larson RA, Boogaerts M, Estey E, Karanes C, Stadtmauer EA, Sievers EL, et al. Antibody-targeted chemotherapy of older patients with acute myeloid leukemia in first relapse using Mylotarg (gemtuzumab ozogamicin). Leukemia, 2002;16:1627-36.
9. Giles F, Garcia-Manero G, Cortes J, Thomas D, Kantarjian H, Estey E. Ursodiol does not prevent hepatic venoocclusive disease associated with Mylotarg therapy. Haematologica, 2002;87:1114-6.
10. Rajvanshi P, Shulman HM, Sievers EL, McDonald GB. Hepatic sinusoidal obstruction after gemtuzumab ozogamicin (Mylotarg) therapy. Blood, 2002;99:2310-4.
11. Alvarado Y, Tsimberidou A, Kantarjian H, Cortes J, Garcia-Manero G, Faderl S, et al. 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.
12. Korth-Bradley JM, Dowell JA, King SP, Liu H, Berger MS. Impact of age and gender on the pharmacokinetics of gemtuzumab ozogamicin. Pharmacotherapy. 2001;21:1175-80.
13. van Der Velden VH, te Marvelde JG, Hoogeveen PG, Bernstein ID, Houtsmuller AB, Berger MS, et al. Targeting of the CD33-calicheamicin immunoconjugate Mylotarg (CMA-676) in acute myeloid leukemia: in vivo and in vitro saturation and internalization by leukemic and normal myeloid cells. Blood, 2001;97:3197-204.