Complete remission in acute myeloid leukemia (AML) with granulocyte colony-stimulating factor without chemotherapy. Report of cytogenetic remission of a t(9;11)(p22q23) positive AML patient and review of literature

Haematologica 2007; 88:(9)e123-e124

In recent years, occasional complete remissions (CR) have been described with G-CSF alone in acute myeloid leukemia (AML).[1-3] Moreover, G-CSF has been proposed as an alternative to donor lymphocyte infusion (DLI) in patients who relapse after allogeneic bone marrow transplantation (BMT).[4-5] We describe an AML patient, carrying the t(9;11)(p22q23), who obtained a cytogenetic CR after treatment with G-CSF alone. A 50 year-old woman was diagnosed with AML, FAB subtype M4. Peripheral blood counts were: WBC 1.2×10^9/L (PMN 15%, Ly 85%), PLT 95×10^9/L, Hb 8.1g/dL. Bone marrow was hypercellular with 60% of blast cells. The karyotype was: 47 XX, t(9;11)(p22;q23), +8. Neither internal tandem duplications nor point mutations of FLT3 were present. Since a perianal abscess was present, it was decided to pre-treat the patient with G-CSF in an attempt to resolve the abscess before induction chemotherapy. A recombinant human G-CSF (lenograstim) was given at a dose of 263 mg/die, corresponding to 3 mg/Kg/day, together with antibiotic. After 14 days of treatment peripheral blood and bone marrow aspirate were normal, and the t(9;11), + 8 clone was no longer detectable. G-CSF treatment was discontinued, and the patient was observed without further treatment until she relapsed 8 months later. Relapse was hematologic and non-hematologic (breast). The morphology of leukemic blast cells and the karyotype were the same as at presentation. G-CSF treatment re-instituted, at the same dose for 5 weeks, but failed to re-induce remission. The remission was then obtained with a combination of high dose arabinosyl cytosine, fludarabine, idarubicin and etoposide. Until now, sixteen (3 APL included) AML and 2 ALL cases, in which CR was achieved with G-CSF alone, have been reported. The characteristics of the previously reported patients are listed in Table 1. In addition, in four cases G-CSF was administered as an alternative to DLI in AML/MDS patients who relapsed after BMT, obtaining CR. Many patients presented with hypoplastic AML and infections. The time to response to G-CSF varied widely; in some cases CR was obtained with no more than two weeks of treatment; in other patients, two or three months of therapy were required. The duration of the response was also variable, ranging from two to more than ten months. A few continuous and 3 cytogenetic CR have been reported. Maintenance therapy with G-CSF was administered in some cases. In two cases, a second and a third CR, respectively, were obtained with G-CSF. No serious adverse events are recorded. It is noteworthy that in one report, G-CSF was successfully administered as a tailored differentiation agent, on the basis of a correlation between a specific chromosomal abnormality, t(8;21), and the response to a specific growth factor, G-CSF.[2] Interestingly, in two cases the ability of G-CSF to induce the neutrophilic differentiation of the leukemic blasts was also demonstrated *ex vivo*. It is unclear why G-CSF as a single therapy can be effective in AML. A few possible explanations can be considered. In the large majority of cases, a concomitant infection was present; it is possible that infection-related cytokines could play a significant role. On the other hand, in a minority of cases, no infection was detected. G-CSF could provide a competitive advantage inducing differentiation of normal hematopoiesis; moreover, a dilution effect of the leukemic clone with a false negative response should be considered. However, considering the sensitivity of cytogenetic analysis, and the durable responses after G-CSF discontinuation, this hypothesis seems unlikely. It has also been suggested that G-CSF could safely induce leukemic blast maturation in hypoplastic leukemia, due to peculiar characteristics of proliferation and differentiation;[3] leukemic cells display hemopoietic growth factor receptors and G-CSF has been described to induce apoptosis of leukemic cells,[6] and not only stimulate clonal proliferation. As regards the t(8;21) AML, the AML-1/ETO fusion protein inhibits the wild type AML-1 gene-directed cell maturation[7] and, interestingly, exposure to G-CSF induces *in vitro* neutrophilic differentiation of blast cells from t(8;21) AML.[8]

Considering the patients relapsed after BMT, the response could possibly be related to the removal of

Table 1. Patients characteristics

Reference	Diagnosis	Disease Status	Infection	G-CSF daily dosage	Therapy duration	Result	CR duration
Yamasaki et al B.J.H. 1991	APL	Resistant	Yes	5 μg/Kg	23 days	CR	n.a.
Yamasaki et al B.J.H. 1991	APL	Resistant	Yes	2.5 μg/Kg	16 days	CR	n.a.
[illegible] et al Leukemia 1992	APL	Untreated	Yes	275-300/kg	7 days	Differentiative effect	
[illegible] et al Acta Haematol 1995	H-ALL	Untreated	No	250μg	15 days	CR	45 days
[illegible] et al Leukemia 1994	H-AML	Untreated	Si	300 μg/Kg	12 days	CR	2 months
Giralt et al NEJM 1994	AML C: +8	Relapsed Post-BMT	No	5 μg/Kg	≤21 days	Cytogenetic CR	10+ months
Giralt et al NEJM 1994	AML C: 20q-	Relapsed Post-BMT	No	5 μg/Kg	≤21 days	Cytogenetic CR	11+ months
[illegible] et al Lancet 1999	H-AML	Untreated	Yes	10 μg/Kg	22 days	CR	2+ months
[illegible] et al B.J.H. 1991	AML C: +4	Resistant to induction	Yes	10 μg/Kg	1 month	CR	1+ month
[illegible] et al Int J Hematol 1995	H-AML	Resistant to induction	Yes	5 μg/Kg	4 weeks	CR	2 years
[illegible] et al BMT 1996	AML	Relapse post BMT	No	5 μg/Kg	55 days	CR	10 months
Takahashi et al Ann Hematol 1997	AML	Untreated	Yes	n.a.	1 months	CR	4 months
Takahashi et al Ann Hematol 1997	AML C: +8	Untreated	Yes	n.a.	18 days	CR C: +8	2 months
Takahashi et al Ann Hematol 1997	AML sec	Untreated	Yes	250μg	1 month	MDS	15 months
Lee et al Int Med 1992	H-AML	Untreated	Yes	n.a.	n.a	CR	n.a.
Takamatsu et al Acta Haematol 1998	H-AML	Untreated	Yes	150 μg/Kg	2 weeks	CR	3 months
Bishop et al [illegible] 2000	AML	Relapse post-BMT	No	5 μg/Kg	3 weeks	CR	10+ months
[illegible] et al B.J.H. 1999	AML C: t(8;21)	Untreated I relapse	No No	450 μg/sqm	2 weeks 2 weeks	I CR II CR	3 months 5 months*
[illegible] et al Leukemia 2001	H-AML C: del 5q	Untreated	No	250μg	8 weeks	Cytogenetic CR	9 months
[illegible] et al Leukemia 2001	H-AML	Untreated	No	250μg	4 months	CR	6 months
[illegible] et al Leukemia 2001	H-AML	Untreated	No	250μg	3 months	CR	4+ months
This report	AML C: t(9;11), +8	Untreated	Yes	5 μg/Kg	2 weeks	Cytogenetic CR	8 months

H-AML: hypoplastic acute myeloid leukaemia
H-ALL: hypoplastic acute lymphoblastic leukemia
AML sec: acute myeloid leukaemia secondary to MDS
C: caryotype
+: persistent condition
*: this patient died while in II CR
[illegible]
n. a. data not available

immunosuppression and a graft-versus-leukemia effect (GVL). Nevertheless, a possible explanation could be direct stimulation on the immune system. In fact, G-CSF administration generally causes a shift of T cells from T_1 to T_2, but the cytotoxic T-cell activity seems to be preserved. In addition, the suppression of proliferation of the abnormal clone or the enhancement of a GVL effect mediated by secondary cytokines could also be possible mechanisms. In the study by Giralt *et al.*, fluorescence in situ hybridization did not show clonal abnormalities in maturing cells, suggesting that the leukemic cells did not differentiate whereas donor cells were stimulated.[5] In our case, a t(9;11)(p22q23) was detected. Truncation of MLL/ALL-1/HRX, the involved gene on 11q23, has been demonstrated to induce a significant inhibition of differentiation with abnormal response to G-CSF. It is possible that in our case a pharmacological dose of G-CSF overcame the differentiation blockade; possibly, at relapse, new undetectable molecular events modified the involved pathway, making G-CSF unsuccessful . It might be interesting to evaluate the effects of G-CSF in AML cells carrying other molecular abnormalities which determine differentiation blockade, such as C/EBPa and FLT3 mutations.[9,10] In conclusion, G-CSF may be useful in selected AML patients, who are not candidates for conventional treatments, especially in the elderly, with normo-hypocellular marrow, and low WBC counts. It may be interesting to investigate the possible role of G-CSF, even in combination with other differentiating agents, in AML cases with specific molecular abnormalities, including FLT3, C/EBPa and MLL mutations. The risk of induction of clonal proliferation should be considered, especially in APL cases, despite few CR being reported in this setting. Additional prospective studies are warranted in order clarify in which setting G-CSF could be most effective, and which schedule should be adopted. Finally, more data are required in order to define the possible role of G-CSF in t(8;21)-positive AML cases.

P.P. Piccaluga, G. Martinelli, M. Malagola, M. Rondoni, M. Bianchini, G. Visani;[1] M. Baccarani
Institute of Hematology and Medical Oncology L. and A. Seràgnoli, S. Orsola-Malpighi Hospital, University of Bologna, Italy;
[1]Department of Haematology, S. Salvatore Hospital, Pesaro, Italy
Correspondence: Pier Paolo Piccaluga, Institute of Haematology and Clinical Oncology Seràgnoli, University of Bologna, Policlinico S. Orsola, Bologna, Italy
Tel: +39-051-6363680 - Fax: +39-051-6364037
Acknowledgments: Supported in part by AIRC, AIL Bologna and Pesaro ONLUS, COFIN 2001 and 2002 (M. Baccarani), Ateneo 2001 and 2002 grants. PPP was also supported by the Associazione Cristina Bassi, Centro Interdipartimentale di Ricerche sul Cancro "Giorgio Prodi" (CIRC) and Rotary International - the Rotary Foundation
Key words: acute myeloid leukemia, granulocyte colony-stimulating factor, t(9;11)(p22q23), MLL, cytogenetic.

References

1. Nimubona, S, Grulois I, Bernard M, Drenou B, Godard M, Fauchet R, et al. Complete remission in hypoplastic acute myeloid leukaemia induced by G-CSF without chemotherapy: report on three cases. Leukemia 2002; 16: 1871-73.
2. Ferrara F, Di Noto R, Viola A, Russo C, Boccuni P, Costantini S, et al. Complete remission in acute myeloid leukaemia with t(8;21) following treatment with G-CSF: flow cytometric analysis of in vivo and in vitro effects on cell maturation. Br J Haematol, 1999; 106: 520-3.
3. Takamatsu Y, Miyamoto T, Iwasaky H, Makino S, Tamura K. Remission induction by granulocyte colony-stimulating factor in hypoplastic acute myelogenous leukaemia complicated by infection. A case report and review of the literature. Acta Haematologica 1998; 99: 224-30.
4. Bishop MR, Tarantolo SR, Pavletic ZS, Lynch JC, Morris ME, Zacharias D, et al. Filgrastim as an alternative to donor leukocyte infusion for relapse after allogeneic stem-cell transplantation. Journal of Clinical Oncology 2000; 18: 2269-72.
5. Giralt S, Escudier S, Kantarjian H, A Esseroth, EJ Freireich, BS Andersson, et al. Preliminary results of treatment with filgrastim for relapse of leukaemia and myelodysplasia after allogeneic bone marrow transplantation. N Engl J Med 1993; 329: 757-61.
6. Fujiwara H, Arma N, Matsushita K, Hidaka S, Ohtsubo H, Fukumori J, et al. Granulocyte colony-stimulating factor induces differentiation and apoptosis of CD2, CD7 positive hybrid leukaemia cells in vivo and ex vivo. Leukemia Res 1997; 21:735-41.
7. Sakamura C, Yamaguchi-Iwai Y, Satake M, Bae SC, Takahashi A, Ogawa E, et al. Growth inhibition and induction of differentiation of t(8;21) acute myeloid leukaemia cells by the DNA-binding domain of PEBP2 and the AML1/MTG8 (ETO)-specific antisense oligonucleotide. Proc Natl Acad Sci USA,1994; 91: 11723-7.
8. Lowemberg B, Touw IP. Hematopoietic growth factors and their receptors in acute leukaemia. Blood 1993; 81: 281-92.
9. Zhang DE, Zhang P, Wang ND, Hetherington CJ, Darlington GJ, Tenen DG. Absence of granulocyte colony-stimulating factor signaling and neutrophil development in CCAAT enhancer binding protein alpha-deficient mice. Proc Natl Acad Sci USA 1997; 94: 569-74.
10. Mizuki M, Schwäble J, Steur C, Choudhary C, Agrawal S, Sargin B, et al. Suppression of myeloid transcription factors and induction of STAT response genes by AML-specific Flt3 mutations Blood 2003; 101: 3164-73.