Recombinant granulocyte-colony stimulating factor as treatment for poor prognosis oligoblastic acute myeloid leukemia in elderly patients

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ABSTRACT

Twenty-five elderly patients with oligoblastic acute myeloid leukemia (AML) received subcutaneous granulocyte colony-stimulating factor (filgrastim) in addition to supportive care. Ninety-two percent of the patients had multilineage dysplasia, 17% hypoplasia, and 48% a high-risk karyotype. During filgrastim treatment neutrophil and platelet counts increased significantly ($p<0.0001$ and ($p=0.042$), respectively) and 3/13 patients (23%) no longer required transfusions. A complete peripheral hematologic response (CHR) was obtained in eight (32%) and marrow blast cell clearance (<5%) in five patients (20%), lasting 12 and 10 months, respectively. Filgrastim caused osteomyalgia and fever in 20% of cases. The median survival was 8 months overall, and 15 months in patients who achieved a CHR. Filgrastim may be a useful adjunct to supportive care in elderly patients with poor-risk AML.

Key words: acute myeloid leukemia, elderly, G-CSF, therapy.

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The prognosis of elderly patients with acute myeloid leukemia (AML) is poor, since the overall median survival of these patients is less than 3 months[1] and under 10% are long-term survivors.[2] In unselected patients, the use of standard chemotherapy has not proven superior to palliative care.[1] Differences in disease biology, including a higher frequency of adverse cytogenetic features,[3] chemoresistant phenotypes,[4] and antecedent myelodysplasia (MDS),[5] likely account for the worse prognosis of elderly patients compared to younger AML patients. Moreover in the majority of elderly patients, conventional chemotherapy has substantial toxicity. Therefore novel and less toxic therapeutic alternatives to conventional chemotherapy should be actively explored. Since some reports have shown that granulocyte-colony-stimulating factor (G-CSF) has antileukemic activity in hypoplastic acute leukemia[6] and in patients with AML who have relapsed after allogeneic stem cell transplantation,[7] we used recombinant G-CSF (filgrastim) to treat elderly patients with poor prognosis AML who were not candidates for conventional chemotherapy.

Design and Methods

Patients with AML diagnosed according to WHO criteria,[8] including AML with multilineage dysplasia and hypoplastic AML, were considered eligible when they were aged over 70 years old, had a peripheral blast cell count $<10.0\times10^9$/L and at least 5% normal bone marrow metaphases. Patients aged 60 to 70 years were also eligible if they had major contraindications to conventional chemotherapy. Patients with low risk AML according to the presence of favorable cytogenetic or molecular abnormalities [inv(16), t(8;21), t(15;17); AML-ETO, PML-RARα, CBFβ-MYH11] were excluded. After obtaining informed consent, filgrastim was given daily by subcutaneous injection at the fixed dose of 300 μg. The dosage was subsequently tapered by reducing the frequency of injections to maintain an absolute neutrophil

count (ANC) >1.5×10⁹/L. No further treatment was given except transient low-dose corticosteroids to improve systemic symptoms in seven patients.

Peripheral blood hematologic parameters were monitored weekly during the first month and then at least monthly. The best peripheral blood hematologic response achieved during filgrastim treatment was evaluated using Cheson's criteria.[9] Bone marrow morphology and cytogenetics were evaluated in all patients at presentation and again in 18 responsive patients. Biopsies were fixed in buffered formalin and treated as previously described.[10] In all cases, immunohistochemical analyses included staining for myeloperoxidase, glycophorin C, LAT (linker for activation of T cells), CD34, TdT and CD117/cKit. Cytogenetic analysis was performed using standard techniques.[3] Treatment was stopped without tapering when either no response, progression during therapy, or major toxicity occurred, or after achievement of a complete response in the marrow without residual myelodysplasia. No maintainance treatment was given. All patients were followed as outpatients with standard supportive measures.

The statistical analyses were performed with Prism4 software. Fisher's exact test or Student's t-test was used when appropriate. Survival probabilities were calculated with the Kaplan-Meier method.

Results and Discussion

Twenty-five patients (22 males and 3 females) entered the study. Eleven patients had previous MDS and three AML secondary to a myeloproliferative syndrome. The clinical characteristics of the patients are summarized in Table 1. Most patients had peripheral blood cytopenia with low peripheral blastosis (median 2%; range 0-26%). At study entry, 40% were febrile and 28% had a documented infection. Marrow cytology was evaluable in 21 cases (1 dry tap; 3 low cellularity), and marrow histology in 23 (1 fibrosis, 1 non-diagnostic specimen), showing hypoplastic AML (marrow cellularity <20%) in four (17.4%). According to the WHO classification, there were 23 cases of AML with multilineage dysplasia, (11 post-myelodysplastic; 9 with trilineage MDS at diagnosis, and 3 post-myeloproliferative disorders), and two cases of AML not otherwise categorized (M2 and M4 according to FAB).[11] Evaluable metaphases were obtained in 21 cases (84 %). Four showed a normal karyotype (19%), seven an intermediate-risk (33.3%), and ten a high-risk karyotype (47.6%).[5] Filgrastim treatment proved to be safe and well-tolerated. In no case did it cause a proliferative effect on the leukemic cell pool, even after prolonged administration. Although G-CSF might theoretically stimulate the proliferation of leukemic cells,[12] myeloid blasts were not responsive to G-CSF stimulation in several studies.[13] Indeed the use of G-CSF is currently approved as supportive therapy in AML patients receiving chemotherapy.[13,14] In all cases treatment could be given on an outpatient basis. Minor side effects included grade 2 osteomyalgia in five patients (20%) and grade 1 fever in two patients (8%) evaluated according to WHO toxicity criteria.[15] Side effects causing treatment interruption included WHO grade 2 fever in the absence of infection in one patient (4%) and mature asymptomatic neutrophilic leukocytosis in two (8%). Five patients (20%) developed documented infections during treatment (tooth abscess n=1, facial cellulitis n=1, esophageal candidiasis n=1 and pneumonia n=2), all of which resolved within 14 days. Only two patients with pneumonia needed admission to hospital. The median treatment duration was 3 months (range: 0.5-18). The median weekly dose of filgrastim actually given was 1295 μg (range: 265-2100). The effects of filgrastim on hematologic parameters are shown in Table 2. Three of 13 patients (23%) became transfusion independent. All neutropenic patients had a response (one minor and 22 major). The mean ANC rose significantly from 0.618×10⁹/L to 4.789×10⁹/L (paired t-test analysis: $p<0.0001$). Six of 13 patients with thrombocytopenia (platelet count <100×10⁹/L) had a major response (absolute platelet count increase of 30×10⁹/L or more or platelet transfusion independence). The mean platelet count increased significantly from 106.9×10⁹/L to 139.9×10⁹/L (paired t-test analysis: $p=0.042$). WHO grade 3 thrombocytopenia developed in one patient with a normal platelet count at baseline. A complete peripheral blood hematologic response (CHR), according to Cheson,[9] defined as hemoglobin >11 g/dL without transfusions, neutrophils ≥1.5×10⁹/L, platelets ≥100×10⁹/L and no peripheral blood blasts, was obtained in eight patients (32%) for a median of 12 months (range: 3-92+), and a partial hematologic response in 17 (68%), lasting a median of 3 months (range: 1-13). This trilineage effect suggests that filgrastim is also active at the level of the pluripotent progenitor cell.[16] Marrow morphology was analyzed after a median of 3 months (range: 1-11) of filgrastim treatment. Blast cell clearance to levels <5% (CR) was documented in five patients (20%), who had also achieved CHR, except for hemoglobin levels between 10.5 and 11.0 g/dL in two. However, pre-existing myelodysplastic features and cytogenetic abnormalities persisted after treatment in 4/4 cases. Likewise, the percentage of CD34⁺, c-kit⁺ and TdT⁺ marrow cells and of CD34⁺ megakaryocytes, evaluated by immunohistochemical techniques in selected cases, did not change significantly. Overall the mean leukemic marrow infiltration decreased not significantly from 33.1% to 23.7%. The percentage of normal metaphases remained unchanged (47.8% vs 48.9%). Marrow CR lasted a median of 10 months (range: 3-91+); relapse occurred while on G-CSF in four of five patients who achieved a CR.

Patients obtaining a peripheral CHR had significantly higher baseline hemoglobin levels (11.6±0.7 vs 9.1±0.6;

Table 1. Clinical and hematologic characteristics of the patients at study entry.

Patients	*N. = 25*
Median age (range)	70 (60-86)
Sex	
male	22 (88%)
female	3 (12%)
Hemoglobin	
mean (g/dL):±SEM	9.9±0.49
anemia (<11 g/dL)	19 (76%)
RBC transfusion need	13 (52%)
ANC	
mean (×10⁹/L)±SEM	0.618±0.087
granulocytopenia (<1.5×10⁹/L)	23 (92%)
infection at study entry	7 (28%)
fever at study entry (>38°C)	10 (40%)
Platelet count	
mean (×10⁹/L)±SEM	106.9±13.9
thrombocytopenia (<100×10⁹/L)	11 (44%)
Peripheral blast cell count:	
mean (×10⁹/L)±SEM	0.149±0.049
Blast cell percentage (median):	
peripheral blood (range)	2 (0-26)
marrow (range)	34 (20-71)
Marrow characteristics	
myelodysplasia	23 (92%)
hypoplasia*	4 (17.4%)
normal metaphases % (range)	50 (6-100%)
high risk karyotype°	10 (47.6%)

**of 23 evaluable cases; °of 21 evaluable cases. RBC: red blood cell; ANC: absolute neutrophil count.*

Table 2. Changes in peripheral blood and marrow parameters during filgrastim treatment.

	Before treatment	*During treatment*	*P*
RBC transfusions (%)	13 (52%)	10 (40%)	NS^
WBC×10⁹/L (mean±SEM)	1.804±0.157	7,773±1.055	<0.0001*
ANC×10⁹/L (mean±SEM)	0.618±0.087	4.789±0.773	<0.0001*
Granulocytopenia (<1.5×10⁹/L)	23 (92%)	0 (0%)	<0.0001^
Platelet count ×10⁹/L (mean±SEM)	106.9±13,9	139,9±20,1	0.042*
Thrombocytopenia (<100×10⁹/L)	12 (44)	8 (32)	NS^
Mean marrow blast cells (%)†	33.1±3.3	23.7±5.6	NS*
Marrow myelodysplasia (%)	23/25 (92%)	14/18 (77%)	NS^
Mean marrow cellularity (%)§	52.7±10.8	58.0±10.5	NS*
Mean normal marrow metaphases (%)°	47.8±8.9	48.9±9.8	NS*

**by paired Student's t test; ^by Fisher's exact test; §of 9 cases with evaluable bone marrow histology reanalyzed; †of 16 cases with evaluable marrow cytology reanalyzed; °of 18 cases with evaluable karyotype reanalyzed; RBC: red blood cell; WBC: white blood cell count; ANC: absolute neutrophil count.*

p=0.012) and a lower peripheral blood blast cell percentage (0.8±0.4% vs 8.1±2.3%; p=0.03), whereas age, white cell count, platelet count, marrow cellularity, marrow blast percentage, dysplasia, normal metaphase percentage and cytogenetic risk class did not predict either CHR or marrow blast cell clearance.

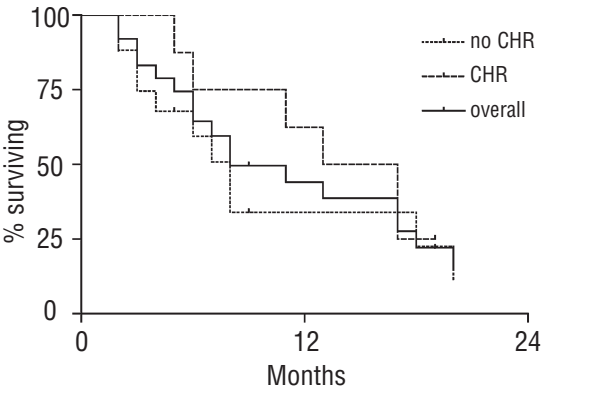

Figure 1. Actuarial overall survival estimates for the whole group of patients receiving filgrastim, and for the subgroups who did or did not achieve a complete peripheral blood hematologic response (CHR) defined as hemoglobin >11 g/dL without transfusions, neutrophils ≥1.5×10⁹/L, platelets >100×10⁹/L, and no peripheral blood blasts.

The persistence of baseline cytogenetic and immunohistochemical abnormalities after treatment[17] suggests that the antileukemic activity of filgrastim is most likely related to a differentiating effect on marrow cells. As recently described, this may explain the short duration of CR.[18] An alternative mechanism of action of filgrastim could be the selective stimulation of normal residual marrow, which may be effective in patients with leukemia relapsing after allogeneic transplantation[7] or in elderly patients with hypoplastic leukaemia,[6] as in our single patient with hypoplastic AML without dysplasia, who has been in unmaintained morphologic and cytogenetic CR for over 93 months. Further theoretical mechanisms of filgrastim activity, such as a modulation of the immune reaction elicited by T-cell subpopulations,[19] or a direct anti-leukemic effect,[20] cannot be excluded.

Three patients were lost to follow-up during treatment after a median of 2 months. Three responsive patients stopped G-CSF treatment because of toxicity, and 16 because of progressive disease after 1 to 15.5 months. G-CSF was also stopped in the only patient who obtained a CR without myelodysplastic features and with normal cytogenetics. One patient was still on treatment. The median actuarial survival was 8 months (range: 2-93+) in the whole group, 15 months (range: 5-93+) in the eight patients who achieved CHR (Figure 1) and 11 months (range: 5-93+) in the five patients who obtained CR in the marrow. Causes of death were leukemia-related in all but one patient, who died of hepatocellular carcinoma. Overall, while on filgrastim, patients spent less than 5% of their lifetime in hospital and their quality of life was acceptable. The median survival of the entire cohort compared favorably with reported figures in similar

groups of patients. While a controlled study is needed to confirm the clinical impression, it should be noted that pancytopenia rather than blastosis is responsible for the majority of clinical problems in these elderly patients. Therefore, the hematologic improvement induced by filgrastim, rather than the complete clearance of leukemic blast cells, may be particularly relevant in modifying patients' life expectancy, as shown by the longer median survival of patients who obtained a complete peripheral hematologic response compared to that of patients with marrow CR (15 vs 11 months). In conclusion, filgrastim may be a useful adjunct to supportive care in elderly patients with poor prognosis AML, and comparative studies as well as a cost-effectiveness analysis may be worthwhile.

Author Contributions

AMP: primary role in study design, acquisition, analysis and interpretation of data, revising content and final approval; MD: secondary role in study design, acquisition, analysis and interpretation of data, revising content and final approval; MD'A: secondary role in study design, acquisition, analysis and interpretation of data, revising content and final approval; MU: secondary role in study design, acquisition, analysis and interpretation of data, revising content and final approval; DM: secondary role in study design, acquisition, analysis and interpretation of data, revising content and final approval; FF: secondary role in study design, acquisition, analysis and interpretation of data; primary role in revising content and final approval; DB: secondary role in study design, acquisition, analysis and interpretation of data, revising content and final approval; SB: secondary role in study design, acquisition, analysis and interpretation of data, primary role in revising content and final approval; GR: primary role in study design, acquisition, analysis and interpretation of data, revising content and final approval.

Conflict of Interest

The authors reported no potential conflicts of interest.

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