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# THERAPEUTIC ACTIONS OF RECOMBINANT HUMAN GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR (GM-CSF)

ARNOLD GANSER AND DIETER HOELZER
Department of Hematology, Johann Wolfgang Goethe-University, Theodor-Stern-Kai 7, D-6000 Frankfurt 70 (Germany)

## BIOLOGY OF GM-CSF

The colony-stimulating factors (CSFs) are glycoproteins which promote and modulate the proliferation and functional activity of various hematopoietic cell populations in vitro and in vivo (1,2). One member of this family is granulocyte-macrophage colony-stimulating factor (GM-CSF) which is a multilineage stimulator preferentially promoting growth and development of neutrophil, monocyte/macrophage and eosinophil progenitor and precursor cells (3-9). Depending on the concentration of GM-CSF in culture, the proportion of cells in cycle, their mean cycle times and the total number of progeny produced are increased (2). With increasing concentration, GM-CSF also becomes an effective stimulator of megakaryocytic and then some erythroid and multipotential progenitor cells (4,6). The effects of GM-CSF on the early progenitors can be enhanced by interleukin-3, interleukin-1, interleukin-6 and G-CSF (10-15).

Apart from its action on progenitor and precursor cells, GM-CSF activates mature, post-mitotic blood cells, increasing phagocytosis, cytotoxicity and superoxide generation by monocytes, neutrophilic and eosinophilic granulocytes as well as the production of prostaglandin-E, gamma-interferon, tumor necrosis factor, plasminogen activator and other CSFs by macrophages (7,16-25). In addition, GM-CSF inhibits neutrophil migration (26-28).

Human GM-CSF is a glycoprotein with a molecular weight of 15-30 Kd depending on the degree of glycosylation. The polypeptide is a single chain of 127 amino acids and a MW of 14.7 Kd (3,29). The gene encoding GM-CSF is located on the long arm of chromosome 5 in close proximity to other grwoth factor genes including interleukin-3, interleukin-4, interleukin-5 and M-CSF (30,31).

GM-CSF exerts its action through binding to high and low affinity GM-CSF receptors which are present in a small number on the membrane of responding hematopoietic cells (32-34). Membrane receptors for GM-CSF are not only present of hematopoietic cells, but also on leukemic cells leading to leukemic cell proliferation

(35-44), as well as on a number of nonhematopoietic cells, such as small-cell lung cancer, ovarian carcinoma and colon-carcinoma cell lines, normal fibroblasts and endothelial cells stimulating in vitro growth and function (45-48). The relevance of these effects in vivo, especially when using GM-CSF after chemo-/radiotherapy for malignant diseases, has not yet been defined.

Normally, GM-CSF is not detectable in the urine or plasma. However, after induction by agents like interleukin-1, endotoxin or foreign antigen, GM-CSF production is highly increased within hours. Sites of production are endothelial cells, fibroblasts, stromal cells, macrophages and T- and B-lymphocytes (49-56).

Recombinant DNA technology has allowed to produce recombinant human GM-CSF in sufficient amounts for preclinical and clinical trials. Human GM-CSF has been expressed in yeast (57,58), Escherichia coli (29) and COS cells (6,59). Carbohydrate moieties are not necessary for either receptor binding or activation, since in vitro and in vivo studies have shown full biologic activity of non-glycosylated GM-CSF (E. coli synthesized) and the partly-glycosylated GM-CSF (produced in yeast) as compared to the fully glycosylated GM-CSF (produced in mammalian cells), but might have some importance in the retardation of clearance and degradation.

## IN VIVO EFFECTS OF GM-CSF

### Pharmacokinetics

After IV bolus injection of recombinant GM-CSF, the initial phase of clearance is between 5-10 minutes (60-62) with a T1/2ß of 85-150 minutes, assuming two phases of elimination. Peak serum concentrations of GM-CSF reached after IV bolus injection of 0.3-1.0 µg/kg or IV infusion over 30 minutes of 10-60 µg/kg range between 14-54 ng/ml and 35-135 ng/ml, respectively (60-62). After IV bolus injections, however, a stimulatory GM-CSF serum concentration >1ng/ml is only maintained for at least twelve hours, if high dosages are administered (62).

In contrast, GM-CSF serum concentrations >3ng/ml can be achieved by either IV continuous infusion of GM-CSF at a dosage of 3µg/kg/day (62) or by SC bolus injection. To obtain a serum concentration >1ng/ml for a prolonged period by SC bolus injection, a GM-CSF dosage above 3 µg/kg/day has to be given (60,63). After SC administration of 10-15 µg/kg, serum concentrations of 5-20

ng/ml are obtained within 2-6 hours which remain >1ng/ml, i.e. in a stimulatory range, for 12-24 hours(60,63,64).

**Hematological Effects**

In patients with malignant disease but not receiving chemotherapy, a significant stimulation of neutrophils, eosinophils and monocytes is observed (60,61,64,65). After an immediate but transient fall in circulating neutrophils, eosinophils and monocytes within 15-30 minutes of IV or SC GM-CSF administration (61,62,64,66), a leukocytosis of up to 10-fold with increases in numbers of circulating neutrophils, eosinophils, monocytes and lymphocytes is observed which is maintained throughout the treatment period but returns to baseline levels within one to two days after the end of GM-CSF application (61,63,64). Granulocytes and monocytes/macrophages are activated after in vivo administration of GM-CSF leading to increased phagocytic activity, monocytic CD11 expression, and release of secondary granules and superoxide anion from neutrophils (61,67-70), while the migration of neutrophils is inhibited (28).

There appears to be a plateau in the increase in neutrophils in the dose range of 3-15 µg/kg/day (71). Continuous IV or SC infusion or SC bolus infection of GM-CSF is more effective than rapid IV infusion (61,71). Optimal doses of GM-CSF in patients not receiving chemotherapy appear to be 250-500 $\mu g/m^2$/day (≈6-12 µg/kg/day), but even doses of 1000 $\mu g/m^2$/day are tolerable, and doses up to 64 µg/kg (≈2500 $\mu g/m^2$/day) have been given (72).

Treatment with GM-CSF results in a dose-dependent increase in bone marrow cellularity and myeloid:erythroid ratio as well as in an increase in eosinophils (64). The cell cylce rate of hematopoietic progenitor cells in the bone marrow is increased within a few days (73-75). Although there is no change in the incidence of progenitor cells in the bone marrow of treated patients, the increase in bone marrow cellularity following treatment with GM-CSF implies that the absolute number of progenitor cells has increased. Similarly, after an initial decrease hematopoietic progenitor cells are recruited into the circulation by administration of GM-CSF, making them accessable for autologous transplantation (75-77).

**Toxicity**

Adverse effects of GM-CSF include mild fatigue, weakness,

fever, bone pain, anorexia, edema, transient dyspnea after the first dose and transient thrombocytopenia. At high dosages which are clinically unnecessary (≈1000 μg/m²) GM-CSF can cause thrombosis, capillary leakage syndrome, effusions, respiratory distress and hypotension. Part of these adverse effects might result from the induction of secondary cytokines, like tumor necrosis factor, interleukin-1 or interleukin-6, and to the induced expression of cell adhesion molecules on leukocytes and endothelial cells (61,64,65,78). Rare adverse effects were the perforation of a granulocytic granuloma within the bowel walls (79). The development of anti-GM-CSF antibodies has been described although these were not neutrolizing (80). Their significance is not yet understood.

Clinical Use of GM-CSF

Treatment of cancer with myelotoxic agents, i.e. chemotherapy or large-field irradiation is accompanied by suppression of normal bone marrow function resulting in anemia, leukopenia or thrombocytopenia. Reversal of profound anemia and thrombocytopenia has usually required transfusion of red blood cells and platelets, while granulocytopenia could generally not be reversed. Especially profound neutropenia with cell counts <500/μl increases the risk of local infection and septicemia. Therefore, it has been general clinical practice to postpone or reduce the amount of myelotoxic chemotherapy in subsequent treatment cycles to prevent the occurence of cytopenia and related morbidity and mortality. This approach, however, increases the risk of a reduced effectiveness of tumorcidal therapy.

There now is an increasing number of studies addressing the issue of reduced myelotoxicity of cancer-chemotherapy by the use of GM-CSF. In general, they have demonstrated the beneficial effect of GM-CSF with tolerable adverse effects. In each of these trials, a dose-dependent decrease of neutropenia was observed with a shortening of the periods of neutropenia and intervals between cycles of chemotherapy (72,81,82). Despite being a multipotential hemopoietic growth factor, the effect of GM-CSF was mainly restricted to the granulocytic lineages with stimulation of the neutrophilic and eosinophilic lineages. However, in a controlled randomized trial (83) as well as two non-randomized trials (62,72) the degree of thrombocytopenia and the requirement

for platelet transfusion were reduced in patients receiving GM-CSF. Stimulation of thrombopoiesis by SC injections of GM-CSF might require a change in the schedule, i.e. dividing the daily dose to two doses every 12 hours appears to be superior to a single daily dosage (84).

While in the non-randomized trial the rate of septicemia was not reduced by GM-CSF (72), less infectious complications (7% versus 24%) were experienced by the patients receiving GM-CSF in the until now only randomized trial (83).

GM-CSF was also used in patients with breast cancer or melanoma (85) and in patients with lymphoid malignancies (86,87) undergoing high-dose combination chemotherapy and autologous bone marrow transplantation. When compared with matched historical controls, leukocyte recovery was fastened, with fewer infections and earlier discharge from hospital. A more rapid platelet recovery, however, was only seen in one trial (86). Additional transfusion of circulating hemopoietic stem cells harvested during prior administration of GM-CSF can even more enhance hematological recovery after autologous bone marrow transplantation (76,88).

In patients with bone marrow failure after allogeneic bone marrow transplantation or unrelated donor transplantation, GM-CSF was effective in improving hematopoiesis and survival in comparison to age-matched controls (89). Similarly, after accidental radiation exposure GM-CSF has been successfully used to improve neutrophil recovery (90).

In a series of trials, GM-CSF has been given to patients with profound neutropenia and increased risk of severe infections, including patients with chronic idiopathic neutropenia (91-93), inherited neutropenia of childhood (94,95), AIDS (96), agranulocytosis (97), aplastic anemia (98-100) or myelodysplastic syndromes (63,64,99,101-105). In patients with chronic idiopathic neutropenia, treatment with GM-CSF has reversed neutropenia during the period of its administration leading to recovery from infections or preventing post-operative wound infections (91). The results in patients with agranulocytosis are diverse. In patients with known underlying mechanism, withdrawal of the offending agent and administration of GM-CSF has fastened neutrophil recovery, while in other patients in whom the underlying cause was unknown and therefore could not be influenced, GM-CSF failed

to reverse neutropenia (97).

A rapid increase in neutrophil and eosinophil counts can be achieved by GM-CSF treatment in leukopenic AIDS patients (96). GM-CSF can also reverse or prevent drug-induced neutropenia which can be pronounced during antiviral therapy with azidothymidine (106) and gancyclovir (107). The modulation of HIV activity by GM-CSF has to be considered which can lead to a rise of p24 levels during therapy with GM-CSF alone. These findings indicate that GM-CSF should be combined with antiviral therapy whenever possible in these patients.

In patients with aplastic anemia, GM-CSF treatment has been successful only in patients with still some residual hematopoiesis in the bone marrow. While these patients responded to administration of GM-CSF with an albeit moderate increase in neutrophil counts (98,99), no response was observed in patients with very severy aplastic anemia, i.e. neutrophil counts below 200/µl (100). These findings indicate that a minimum number of stem cells have to be left in the bone marrow to obtain a hematopoietic response to the administration of GM-CSF.

Several clinical trials with rhGM-CSF in patients with myelodysplastic syndromes have been published to date including a total of 55 patients (63,99,101-104). Of these patients who were treated with different schedules, GM-CSF dosages and routes of administration, 84% showed a dose dependent increase in neutrophil counts. An increase in reticulocyte counts was observed in 38% of the patients. Platelets increased above baseline values in 15% of the patients. In eleven patients (20%), a transient increase in the marrow and/or peripheral blood blast cells was noted. Nine of the patients, particularly those with >15% bone marrow blasts, progressed to acute leukemia.

In the only randomized trial, patients with myelodysplastic syndromes received either 3 µg/m²/day GM-CSF SC or were observed (105). With more than 25 patients in each arm and treatment periods in excess of six months, all patients receiving GM-CSF had a sustained increase in neutrophil counts coupled with a decrease in infection rate. No effect was seen on the platelet or reticulocyte counts. Progression to acute leukemia was comparable in both arms totalling to about 10% each.

The substantial rise in neutrophils in patients with only ab-

normal metaphases in the bone marrow can be regarded as evidence that GM-CSF in some cases acted as an agent which in vivo can induce maturation of malignant myeloid cells (101,102). Premature chromosome condensation analysis of maturing granulocytes also indicate that the neoplastic precursor cells rather rather than normal hemopoietic progenitor cells are stimulated to differentiate (108). This is further supported by results from analysis of X-linked restriction fragment length polymorphism in a female patient with refractory anemia heterozygous for the X-chromosome linked gene pyruvate glycerol kinase (Ganser et al, submitted). Despite a response of the neutrophil counts to GM-CSF, the bone marrow and peripheral blood cells in this patients remained clonal. In contrast, Vadhan-Raj et al (109) recently published data showing that an individual patient with therapy-related myelodysplastic syndrome and pancytopenia achieved complete hematologic, cytogenetic and molecular genetic remission for nearly 1 year after discontinuation of GM-CSF.

As clinical studies in patients with myelodysplastic syndromes but increased blast cell load have shown, GM-CSF is capable of recruiting leukemic blast cells into proliferation in vivo. GM-CSF has therefore been used in combination with low-dose cytosin-arabinoside (110,111): first, because there is ample experience that low-dose cytosin-arabinoside alone can achieve responses in myelodysplastic syndromes (112), and second, because there is evidence for a synergistic effect with GM-CSF (113-117). Similarly, hematopoietic growth factors might be particularly useful for recruiting quiescent leukemic stem cells into cell cycle rendering them more sensitive to chemotherapeutic agents and increasing the log kill of the malignant clone. Preliminary results of ongoing trials demonstrate the feasability of this approach, but randomized trials will have to show whether the rate of complete remissions and the remission duration can be improved.

## Conclusion

The initial data of the clinical trials suggest that GM-CSF is a potent stimulator of blood formation which can be used to alleviate chemotherapy/radiotherapy induced bone marrow suppression. Ongoing and future clinical trials will have to show whether the tumoricidal therapy can be dose-intensified to in-

crease the response rates and remission duration periods. Future trials are also likely to use combinations of the growth factors to obtain multilineage hematopoietic responses.

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Discussion - THERAPEUTIC ACTIONS OF RECOMBINANT HUMAN GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR (GM-CSF)

A.J.H. Gearing

The toxicities you see, with GM being more potent in toxicity than IL3 and IL3 being more than GCSF, seem to correlate with the ability to stimulate IL1 release, at least in vitro. Do you think that is reasonable?

A. Ganser

We monitored our patients checking for TNF alpha levels, IL1 levels and IL6 levels. The only cytokine we could detect was IL6 in patients developing fever. I think it is awfully difficult to detect them because where the cytokines are working is in the bone marrow or at the end organ, and one can never find IL1 or increased TNF alpha levels in the serum. I think that either their turnover in serum is too fast, as once they are released into the circulation they are taken up by the end organs, or they are not even released into the serum.

L. Gauci

One of the major concerns outside the oncology community, is the desire to use hematopoietic growth factors to allow for the increase in the amount of chemotherapy that can be given. This will certainly precipitate other serious toxicities. I think this is potentially very dangerous however it has to be tried, but should be done only by experimented research physicians. The risks are too great to permit indiscriminated usage.

A. Ganser

The hopes concerning the possibility of using greater amounts of chemotherapy were too exaggerated. For instance, one can increase the amount of adriamycin by about 50%, but then you reach toxic levels in other organs, and you have to stop there.

D. Maruhn

You mention the reduction of application of antibiotics as one of the possible advantages of administration of these drugs. Is that substantiated by any data?

A. Ganser

There are several randomized trials, both after chemotherapy and after autologous bone marrow transplantation. The multi center European trial using GM-CSF shows a shortening of the duration of neutropenia by about one week and thus the isolation time in hospital and in the laminar air flow rooms can be shortened by about one week.

J. Bigorra

It is said that interleukin 3 increases the number of platelets. Do you know if these data come in trials done in healthy volunteers or in patients, and if it was done in healthy volunteers, do you have experience in patients?

A. Ganser

The interleukin 3 phase I trial was done in patients with solid tumours but with normal bone marrow function. And we also used interleukin 3 in patients with depressed bone marrow function after previous prolonged chemotherapy or bone marrow infiltration by solid tumour cells. We have treated 10 of these patients and in 8 of them platelet counts improved. This improvement lasted for prolonged periods: even if you give it only for fifteen days, the improvement lasts for several months. Some of the patients had even been GM-CSF failures. We also used it in patients with myelodysplastic syndromes, but it is not that good in that subset of patients. Some of the patients got an improved platelet count but that was not overwhelming. Also in patients with aplastic anemia, results were quite disappointing. But I think from the data raised in patients with normal bone marrow function, that it is appropriate to combine immunosuppressive therapy and cytokine therapy in certain cases, for instance in patients with aplastic anemia.