S-11-B-1 Clinical Use of Recombinant Human G-CSF.

Aplastic Anemia (AA) and Myelodysplastic Syndromes (MDS)

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I. INTRODUCTION

Myelodysplastic syndromes (MDS) and aplastic anemia (AA) have one feature in common that both are hematopoietic stem cell disorders. Consequently, patients with MDS and AA usually suffer from pancytopenia which lasts for months or years. In fact, infections due to neutropenia are difficult to manage and may occasionally be lethal in these disorders. Dysfunctions of neutrophils are additional factors contributing to the high incidence and severity of bacterial infections in MDS. We wanted to ask if granulocyte colony-stimulating factor may improve neutropenia in these clinical settings.

II. STUDY DESIGN

In an early phase II trial of a glycosylated recombinant human granulocyte colony-stimulating factor (rh G-CSF), 24 patients with MDS and 30 patients with AA were given a daily dose of 2, 5, 10 and 20 µg/Kg, either intravenously or subcutaneously, for at least 7 days. Responders received the same dose for an additional 7 days, while nonresponders received escalating doses after a rest period of 3 days.

On the basis of the 7 day trial, a dose of 5 µg/Kg was selected and administered daily for 14 days in an additional 37 patients (19 with MDS and 18 with RA). At enrollment either in the 7 day or 14 day trials, most patients were severely neutropenic with the blood neutrophil counts less than 500/µl (61 % and 73 % in the 7 day and 14 day trials, respectively). Thirty % and 21.6 % of the patients had blood neutrophil counts ranging from 500 to 1,000/µl in the 7 day and 14 day trials, respectively.

III. DOSE RESPONSE IN SEVEN DAY TRIAL

1. MDS

As assessed by the peak neutrophilic responses, most MDS patients responded to the 3 dose levels (2 $\mu\text{g}/\text{Kg}/\text{day}$, 5 $\mu\text{g}/\text{Kg}/\text{day}$ and 10 $\mu\text{g}/\text{Kg}/\text{day}$) irrespective of the French-American-British (FAB) subclassification of MDS [1]. Some patients with low pretreatment neutrophil counts ($\leq 100/\mu\text{l}$) failed to respond even at high dose ranges while others with similarly low neutrophil counts did respond [2]. Thus, low neutrophil counts prior to treatment did not preclude the potential to respond to rh G-CSF. In addition, the peak neutrophil counts were higher at 5 $\mu\text{g}/\text{Kg}/\text{day}$ than at 2 $\mu\text{g}/\text{Kg}/\text{day}$.

2. AA

In contrast to MDS, there were some nonresponders to rh G-CSF in AA patients at all doses examined. Most of these nonresponders had low pretreatment neutrophil counts. In this regard, we arbitrarily defined responders among AA patients as follows: patients whose neutrophils increased from a pretreatment level of $<500/\mu\text{l}$ to a peak greater than $500/\mu\text{l}$ and patients whose neutrophils increased from pretreatment levels of $<1,000/\mu\text{l}$ to a peak greater than $1,000/\mu\text{l}$. Moreover, neutrophilic increment induced by G-CSF was found to correlate with the pretreatment neutrophil counts. In general, the lower the initial values, the lower the responses.

Fig. 1. Changes in the blood neutrophil counts in patients with aplastic anemia receiving rh G-CSF in the 14 day trial.

IV. FOURTEEN DAY TRIAL

1. MDS

Mean blood neutrophil counts started to increase immediately after the first dose, remained at significantly elevated levels (1,000 to 3,000/ μ l) during the treatment course in MDS and returned to the baseline levels within one week after discontinuation [2].

2. AA

On the other hand, AA patients varied widely in their responses to rh G-CSF therapy depending on the pretreatment neutrophil counts. Thus, the mean daily neutrophil counts remained virtually unchanged in the nonresponders, while the daily neutrophil counts of the responders were elevated during the course of treatment (Fig. 1).

3. Adverse effects

Adverse effects included fever, injection site reaction, skin eruption and thrombocytopenia. But they were mild and rare [2].

V. SIGNIFICANCE

The results showed that rh G-CSF at a daily dose of 5 μ g/Kg would be effective in improving the neutropenia of MDS and AA patients. The effect was specific for and confined to neutrophils. No consistent changes were found in blood cells other than neutrophils. Moreover, rh G-CSF did not stimulate proliferation of marrow blast cells in the majority of MDS patients [2], although a possible stimulation of MDS blast cells was the major concern in the clinical application of colony-stimulating factors.

Colony-stimulating factors are unique in that they not only induce differentiation, but also stimulate the growth of hematopoietic progenitor cells. However, in the context of differentiation induction, cellular differentiation may be obtained only at the same time when there is a possible growth promotion of the abnormal clones. The lineage specific G-CSF has greater differentiation inducing potential than the earlier and more broadly acting factors such as granulocyte-macrophage CSF (GM-CSF) or multi CSF. This notion was supported by the findings of increased marrow myeloid maturation, increased myeloid/erythroid ratios and the persistence of cellular dysplasias and cytogenetic abnormalities [2].

An additional advantage of G-CSF is the possible enhancing effects on neutrophil functions [3]. Since the treatment duration was rather short, our results suggest, but not prove, if rh G-CSF therapy would be effective in the treatment of infection or even its prophylaxis. The half life of G-CSF in the circulation is longer when it is given via subcutaneous rather than intravenous route. In the present study, almost comparable results were obtained in a small number of patients given subcutaneous injections of rh G-CSF. However, the effects were generally confined to the duration of rh G-CSF administration. Clearly, a more prolonged course of rh G-CSF therapy is needed to know whether patients with MDS and AA keep responding to the maintenance dose of rh G-CSF.

In conclusion, G-CSF may have less risk of blast cell proliferation while retaining the capacity to stimulate granulocyte production and to activate granulocyte functions. Future studies should be directed to the maintenance administration using subcutaneous injection to determine whether such prolonged treatment may lead to sustained elevation of the blood neutrophil counts in MDS and AA and thereby result in a decreased risk of developing infections.

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