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Effect of Recombinant Granulocyte-Macrophage Colony-Stimulating Factor (GM-CSF) on Leukopenia in AIDS: A Study of Seven Cases

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Summary and Key Words

Seven neutropenic patients with the acquired immunodeficiency syndrome (AIDS) or AIDS-related complex (ARC) were treated with recombinant human GM-CSF in an attempt to reverse their leukopenia. Overall, treatment was associated with a rapid, substantial increase in neutrophilic granulocytes and a smaller increment in eosinophils and monocytes. No significant increase in platelets or reticulocytes was observed. Termination of treatment was associated with a rapid drop in the leukocyte count. While some patients with severely hypoplastic marrows did not respond to GM-CSF treatment, azidothymidine- or ganciclovir-induced neutropenia was reversed by concomitant administration of GM-CSF in others. This indicates that rhGM-CSF may be a valuable adjunct to antiviral therapy in ARC/AIDS and requires further testing in controlled trials.

Infection with the human immunodeficiency virus (HIV) leads to a destruction of the immune defense system resulting in various opportunistic and viral infections [1, 2]. Granulocytopenia, anemia and thrombocytopenia as additional hematologic manifestations of the HIV-infection [3, 4] frequently preclude the use of antiviral, antibiotic and antineoplastic agents which by themselves are myelosuppressive. For example, administration of AZT, ganciclovir (DHPG) and trimethoprim sulfamethoxazol (Bactrim), is associated with severe hematotoxicity in the majority of patients [5–7]. Recombinant human granulocyte-macrophage colony-stimulating factors (CSF), (rhGM-CSF) stimulates multipotential and various lineage restricted progenitor cells in vitro, and enhances the functional activity of mature granulocytes and monocytes, and may thus function as an integral part of the host’s response to infectious and immunological challenge [8]. In patients with the acquired immune deficiency syndrome (AIDS), administration of rhGM-CSF resulted in a dose-dependent increase of peripheral blood leukocyte counts which persisted during the period of administration [9]. In a separate study of severely neutropenic patients with CMV-retinitis, the concomitant administration of rhGM-CSF mitigated the leukopenia and facilitated prolonged treatment with ganciclovir with prevention of progression of retinitis in virtually all patients [10]. This evidence supporting a beneficial effect of rhGM-CSF on the hemopoietic function in patients infected with HIV provided the rationale for treating neutropenic patients with ARC/AIDS with rhGM-CSF in an attempt to reverse their leukopenia.

Patients and Methods

Patients above 18 years of age with a proven HIV-infection were eligible for the study after having given informed written consent; the study was approved by the local ethics committee. Six of the seven currently evaluable patients (five male, two female) had AIDS, one patient was in the stage of ARC. The median age was 37 years with a range of 29 to 54 years (Table 1). Cause of the leukopenia was prior administration of AZT (n=2), DHPG (n=3), Cotrimoxazol (Bactrim), is associated with severe hematotoxicity in the majority of patients [5–7]. Recombinant human granulocyte-macrophage colony-stimulating factors (CSF), (rhGM-CSF) stimulates multipotential and various lineage restricted progenitor cells in vitro, and enhances the functional activity of mature granulocytes and monocytes, and may thus function as an integral part of the host’s response to infectious and immunological challenge [8]. In patients with the acquired immune deficiency syndrome (AIDS), administration of rhGM-CSF resulted in a dose-dependent increase of peripheral blood leukocyte counts which persisted during the period of administration [9]. In a separate study of severely neutropenic patients with CMV-retinitis, the concomitant administration of rhGM-CSF mitigated the leukopenia and facilitated prolonged treatment with ganciclovir with prevention of progression of retinitis in virtually all patients [10]. This evidence supporting a beneficial effect of rhGM-CSF on the hemopoietic function in patients infected with HIV provided the rationale for treating neutropenic patients with ARC/AIDS with rhGM-CSF in an attempt to reverse their leukopenia.

Results and Discussion

Patients above 18 years of age with a proven HIV-infection were eligible for the study after having given informed written consent; the study was approved by the local ethics committee. Six of the seven currently evaluable patients (five male, two female) had AIDS, one patient was in the stage of ARC. The median age was 37 years with a range of 29 to 54 years (Table 1). Cause of the leukopenia was prior administration of AZT (n=2), DHPG (n=3), Cotrimoxazol and no treatment immediately prior to the study, respectively. RhGM-CSF (Behringwerke AG, Marburg, FRG) was expressed in yeast and given at a dose of 150 μg/m² as a daily i. v. infusion over 8 hours. Three patients received one, and four patients received 2 treatment cycles; the duration of each cycle ranged from two to 25 days (Table 2).
Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Number of Patients</th>
<th>7</th>
</tr>
</thead>
<tbody>
<tr>
<td>male/female</td>
<td>5/2</td>
</tr>
<tr>
<td>Age (years): median</td>
<td>37</td>
</tr>
<tr>
<td>range</td>
<td>(29-54)</td>
</tr>
<tr>
<td>Stage:</td>
<td></td>
</tr>
<tr>
<td>ARC</td>
<td>1</td>
</tr>
<tr>
<td>AIDS</td>
<td>6</td>
</tr>
<tr>
<td>Concomitant therapy:</td>
<td></td>
</tr>
<tr>
<td>AZT</td>
<td>3</td>
</tr>
<tr>
<td>DHPG</td>
<td>2</td>
</tr>
<tr>
<td>Cotrimoxazol</td>
<td>1</td>
</tr>
</tbody>
</table>

ARC: AIDS-related complex; AIDS: acquired immunodeficiency syndrome; AZT: azidothymidine; DHPG: Ganciclovir.

from 1115±174/μl to 4521±100/μl (mean ± SEM). The effect of rhGM-CSF on the different leukocyte subpopulations and the response kinetics are exemplified in figure 1: there was a small increment in bands, eosinophils and monocytes, the major response resulting from the increase in mature neutrophils. There was no significant increase in platelets or reticulocytes. Typically, the increase in WBC was rapid, occurring within a few days of rhGM-CSF administration; after termination of treatment, there was a rapid decline of the WBC. Essentially no response was seen in three patients who received one treatment cycle (F10, F14, F15) and during the first of two cycles in one additional patient (M2) (Table 2). While rhGM-CSF was given for only 2 days in one of these patients, the lack of response can not be attributed to an insufficient treatment duration in the others. All of these patients had severely hypoplastic bone marrows, however, suggesting that the degree of pre-existing bone marrow damage may determine the response to rhGM-CSF. In addition, AZT or Cotrimoxazol given as concomitant medication during the treatment could have been responsible for the lack of hematological response. Since progenitor cells in AIDS have been shown to be more sensitive to inhibition by AZT and appear to require higher concentrations of GM-CSF than progenitors from healthy controls [11-13], some initially unresponsive leukopenic patients receiving AZT might have benefitted from rhGM-CSF administration at a higher dose level. The feasibility of reversing granulocytopenia during concomitant treatment with myelotoxic antiviral agents is clearly demonstrated by the patients receiving DHPG (M3, M4) or AZT (M2) (Table 2), each of whom responded with a pronounced increase of granulocytes during two successive cycles of rhGM-CSF, with a return to near baseline levels after termination of rhGM-CSF. Mild fever and prostration (WHO-grade I-II) were the predominant side effects. More severe reactions (fever to 40°C, chills and rigors) were observed only rarely and appeared to occur primarily in patients with concurrent infections. Since GM-CSF given alone might potentiate viral production in monocytes yet enhances the antiviral activity of AZT [14], GM-CSF therapy should probably be combined with AZT whenever possible.

Overall, these data in addition to the results reported by Groopman et al. [9] indicate that rhGM-CSF is a potentially valuable adjunct to antiviral therapy in patients with ARC/AIDS, and requires further testing in controlled trials.

Table 2. Response to treatment with rhGM-CSF

<table>
<thead>
<tr>
<th>Pat.</th>
<th>Dose</th>
<th>Days</th>
<th>WBC/μl before</th>
<th>Neutroph./μl before</th>
</tr>
</thead>
<tbody>
<tr>
<td>F10</td>
<td>150</td>
<td>2</td>
<td>1.4</td>
<td>1.7</td>
</tr>
<tr>
<td>F14</td>
<td>150*</td>
<td>10</td>
<td>1.2</td>
<td>1.8</td>
</tr>
<tr>
<td>F15</td>
<td>150*</td>
<td>8</td>
<td>2.4</td>
<td>2.6</td>
</tr>
<tr>
<td>M1</td>
<td>150*</td>
<td>25</td>
<td>1.5</td>
<td>11.2</td>
</tr>
<tr>
<td>M2</td>
<td>150**</td>
<td>5</td>
<td>1.9</td>
<td>8.4</td>
</tr>
<tr>
<td>M3</td>
<td>150***</td>
<td>14</td>
<td>1.2</td>
<td>4.6</td>
</tr>
<tr>
<td>M4</td>
<td>150***</td>
<td>14</td>
<td>0.9</td>
<td>6.7</td>
</tr>
<tr>
<td>M5</td>
<td>150***</td>
<td>14</td>
<td>1.2</td>
<td>7.9</td>
</tr>
</tbody>
</table>

Concomitant medication: *AZT; **Cotrimoxazole; ***DHPG

References

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