Brief Communication

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Is Aciclovir Prophylaxis Necessary After Bone Marrow Transplantation?

Summary: To assess the cost-effect relationship of aciclovir prophylaxis versus early treatment, we performed a retrospective study in 44 allogeneic bone marrow transplant recipients, who had only received aciclovir for therapeutic purposes. After bone marrow transplantation 18 herpes simplex infections occurred in 15 of the 33 patients who were seropositive for herpes simplex virus. In ten patients without clinical signs, routine viral cultures yielded herpes simplex virus. Aciclovir was given intravenously to the patients with mucocutaneous herpes infection. All infections responded rapidly. It can be calculated that restricting the drug to therapeutic use reduced the amount of aciclovir used, which in turn diminished the cost of treatment and the risk of aciclovir resistance.


Introduction

Following allogeneic bone marrow transplantation, 40-80% of patients with antibodies to herpes simplex virus develop a mucocutaneous herpes simplex infection (1-3). In some patients, this may lead to serious complications, especially (lethal) pneumonitis. Several groups have reported on the efficacy of aciclovir in the prevention of herpes simplex virus infections in bone marrow transplant recipients (2-4), while other authors have discussed earlier engraftment (5, 6) and milder grades of acute graft versus host disease (GHVD) in patients receiving methotrexate as GHVD prophylaxis (4) in this context. We question the need for aciclovir prophylaxis in all herpes simplex virus-seropositive bone marrow transplant patients in view of the effectiveness of aciclovir for treatment. To assess the cost-effect relationship of aciclovir in bone marrow transplant patients, we performed a retrospective study in 44 allogeneic bone marrow transplant patients who had only received aciclovir for therapeutic purposes.

Patients and Methods

Patients: Between September 1979 and September 1984, 44 patients were given HLA-identical, MLR-negative sibling bone marrow for the treatment of acute leukemia in remission (n = 41) or chronic myelogenous leukemia in the chronic phase (n = 3). The patients were prepared for transplantation as described elsewhere (7). Engraftment was said to have occurred on the first day on which the number of peripheral blood neutrophils was greater than 0.1 × 10⁹ cells/l. Acute GVHD was diagnosed and staged on the basis of the clinical criteria defined by Thomas et al. (8).

Diagnosis and treatment of herpes simplex virus infection: Viral culture of throat swabs was performed on a weekly basis during hospitalization, and additional cultures were taken when herpes simplex virus-suspect lesions appeared. Herpes simplex virus was isolated by inoculation of human diploid fibroblasts. Herpes simplex virus antibodies were determined by immune adherence hemagglutination (9). Administration of aciclovir was started when mucocutaneous herpes simplex virus infection was suspected on clinical grounds. Aciclovir was given i.v. three times daily at a dosage ranging from 15 to 25 mg/kg/day for periods of between five and 14 days. If necessary, the dose was adjusted to renal function according to the regimen proposed by Blum et al. (10).

Results

Incidence of Herpes Simplex Virus Infection

Thirty-three of the 44 bone marrow transplant patients were seropositive prior to bone marrow transplant. After
The median time to engraftment was 13 days (range: 7–27 days). In 36 patients who did not receive aciclovir before engraftment, the median time to engraftment was 13 days (range: 7–20 days), and in eight patients given aciclovir before engraftment the median time was also 13 days (range: 11–27 days; \( p = 0.3 \), Wilcoxon’s rank test).

**Influence of Aciclovir on Acute GVHD**

Of the 44 patients, 31 developed GVHD. Two patients could not be evaluated because they died within a month after bone marrow transplantation, but without evidence of GVHD. Of the patients who received aciclovir in the first month after bone marrow transplantation (\( n = 12 \)), five had grade 0–I GVHD. The median time of onset of GVHD in these 12 patients was day 30 (range: 18–54 days). Thirty patients did not receive aciclovir in the first month post-bone marrow transplant; ten of these did not develop GVHD, and three developed only grade I (days of onset: 7, 32 and 33). Seventeen patients showed severe GVHD (grade II–IV) after a median time of 25 days (range: 16–36 days) after bone marrow transplant (\( \chi^2 = 0.01, p = 0.9367 \)).

**Discussion**

In this study, 75% of the 44 bone marrow transplant patients were seropositive for herpes simplex virus. During the first 40 days post-bone marrow transplant, clinically diagnosed herpes simplex virus infection occurred in 47% of the seropositive patients and in none of the seronegative patients. The incidence of recurrence of herpes simplex virus in treated patients is lower for our series than in those of others (2, 4, 6), who reported 73%, 82% and 80%, respectively. In our series, herpes simplex virus infections were remarkably free of complications. Generalization was observed in one patient, but organ involvement did not occur. Since we did see complications of herpes simplex virus infection in the pre-aciclovir era, it seems probable that early aciclovir therapy is capable of preventing them. It has been reported that aciclovir prophylaxis tends to lessen the severity of GHVD (4) and to promote engraftment (6). In our study we found no evidence to indicate milder GVHD or earlier engraftment in patients given aciclovir in the first month after bone marrow transplantation. However, our patients received aciclovir later and over a shorter period of time than those of Gluckman et al. and Wade et al. On the basis of our experience, we consider it unnecessary to give aciclovir prophylaxis to seropositive bone marrow transplant patients. Our calculations show that restricting the drug to therapeutic use reduced the amount of aciclovir used, which in turn diminished not only the cost of treatment but also the risk of aciclovir resistance (11).

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**Table 1: Calculated amounts of aciclovir needed for therapy and prophylaxis in bone marrow transplant patients.**

<table>
<thead>
<tr>
<th>Indications</th>
<th>No. of patients</th>
<th>Aciclovir for i.v. therapy (g)</th>
<th>Aciclovir for prophylaxis (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical herpes simplex virus</td>
<td>15</td>
<td>178</td>
<td>i.v.*</td>
</tr>
<tr>
<td>Clinical herpes simplex virus and/or positive cultures</td>
<td>22</td>
<td>223</td>
<td>–</td>
</tr>
<tr>
<td>All seropositive patients</td>
<td>33</td>
<td>–</td>
<td>743</td>
</tr>
<tr>
<td>All patients</td>
<td>44</td>
<td>–</td>
<td>990</td>
</tr>
</tbody>
</table>

* 500 mg Aciclovir three times daily for 15 days (8);
** 400 mg Aciclovir five times daily for 30 days (11).

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**Calculation of the Total Amounts of Aciclovir**

We calculated the amount of aciclovir that would have been given during the first 40 days following bone marrow transplant, either for treatment or as prophylaxis in herpes simplex virus infection (Table 1). In the present study our patients received 148 g aciclovir during the first 40 days after bone marrow transplant. If we take into account the three episodes that were not treated because of a temporarily limited supply of aciclovir, this amount would have been 178 g. Had all 33 seropositive patients been treated with aciclovir prophylactically according to the regimens proposed by Saral et al. (2) or Wade et al. (6), the amount of aciclovir given would have been four or eleven times greater, respectively.
Literature


Infection 14 (1986) Nr. 3 © MMV Medizin Verlag GmbH München, München 1986