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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.

Zusammenfassung: *Ist nach Knochenmarkstransplantation eine Aciclovir-Prophylaxe nötig?* Bei 44 Empfängern von allogenen Knochenmarkstransplantaten, die Aciclovir ausschließlich therapeutisch erhalten hatten, wurde eine retrospektive Studie durchgeführt, um die Kosten-Nutzen-Beziehung für die Prophylaxe im Vergleich zur Frühtherapie zu bestimmen. Bei 15 der 33 Herpes-simplex-Virus-seropositiven Patienten traten nach Knochenmarkstransplantation 18 Herpes-simplex-Virus-Infektionen auf. Bei zehn klinisch symptomfreien Patienten wurde in Routinekulturen Herpes-simplex-Virus nachgewiesen. Patienten mit mukokutaner Herpesinfektion erhielten Aciclovir intravenös appliziert. Alle Infektionen sprachen rasch auf die Therapie an. Es läßt sich errechnen, daß eine Beschränkung auf den therapeutischen Einsatz des Medikamentes den Verbrauch von Aciclovir vermindert und somit die Behandlungskosten und das Risiko der Resistenzentwicklung gegen Aciclovir erniedrigt.

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 0.1×10^9 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

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

Indications	No. of patients	Aciclovir for i.v. therapy (g)	Aciclovir for prophylaxis (g)	
			i.v.*	oral**
Clinical herpes simplex virus	15	178	–	–
Clinical herpes simplex virus and/or positive cultures	22	223	–	–
All seropositive patients	33	–	743	1980
All patients	44	–	990	2640

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

bone marrow transplant, 18 episodes of herpes simplex virus infection were diagnosed clinically in 15 of these seropositive patients. The median time of infection was 14 days (range: 1–113 days). No infections occurred in the group of seronegative patients. Three patients had a second episode of herpes simplex virus infection between days 69 and 86. Of the 18 herpes simplex virus episodes, 11 were confirmed by positive cultures. The routine viral cultures were positive in seven patients without clinical signs, the median time being 24 days (range: 7–127 days). In addition, of the three patients who showed a four-fold rise in herpes simplex virus antibody titer, two had negative cultures and no clinical signs of herpes simplex virus infection. Only one patient developed a generalized herpes simplex virus infection of the skin; in this case aciclovir therapy led to a complete recovery. None of the herpes simplex virus infections resulted in a fatal outcome in this series.

Therapy with Aciclovir

Of the 18 episodes of clinically diagnosed herpes simplex virus infection, 15 were treated with aciclovir during a median period of seven days (range: 5–14 days). The median total amount of aciclovir given per patient was 7 g (range: 3.5–20 g). All patients showed regression of the lesions within six days after the initiation of therapy. Aciclovir was not given during three of the episodes because the drug was not readily available at the time; all three ended in spontaneous recovery.

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.

Influence of Aciclovir on Engraftment

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 GHVD (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 GHVD 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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