To the editor:

Cidofovir for cytomegalovirus-preemptive therapy in stem cell transplant recipients

Ljungman et al[1] recently reported the results of a survey of the European Group for Blood and Marrow Transplantation (EBMT) regarding efficacy and toxicity of cidofovir in allogeneic stem cell transplant recipients. They observed a response to cidofovir in 50% of patients treated for cytomegalovirus (CMV) disease, in 66% of patients who failed or relapsed after preemptive therapy, and in 62% of patients receiving cidofovir as primary preemptive therapy. From these data, those authors concluded that cidovofir can be effective in the treatment of CMV infection and disease after allogeneic stem cell transplantation and is associated with an acceptable risk of toxicity. Furthermore, they stated that cidofovir can be considered in patients with CMV disease as second-line preemptive therapy.

The data of our single-center prospective study on cidofovir as first-line preemptive therapy in allogeneic stem cell transplantation significantly contradict this encouraging and optimistic point of view. So far, we have treated 21 patients using a dosage of 5 mg/kg of body weight once a week for the first 2 weeks, followed by one application every other week. Therapy was continued until CMV polymerase chain reaction (PCR) and/or pp65 antigenemia was negative for at least 3 consecutive weeks. Patient characteristics are depicted in Table 1. These patients were not include in the EBMT survey by Ljungman et al[1] because of their participation in our ongoing study. All patients received probenecid and prehydration according to manufacturer's recommendations. Patients were routinely monitored for CMV by PCR and pp65 twice a week if leukocyte counts exceeded 500/μL. CMV disease was defined according to published recommendations.[2] For the diagnosis of CMV pneumonia, clinical signs of pneumonia, together with virus detection in the bronchoalveolar lavage fluid (BAL), were required. Failure of preemptive therapy was defined as continued presence of PCR-positive signal and/or pp65 antigenemia.

Out of 21 patients, 1 patient responded to cidofovir and demonstrated a conversion to a negative PCR signal remaining negative for at least 3 weeks after discontinuation of therapy. Fifteen patients became CMV PCR negative after 2 weeks of therapy, but a positive signal in the CMV PCR was again observed 2 to 3 weeks later during maintenance therapy. Five patients failed to respond to cidofovir as determined by a continuous positive CMV PCR signal. In the nonresponsive patients, as well as in the patients converting from a negative signal to a positive signal during maintenance therapy, antiviral therapy was changed to ganciclovir. In 14 of these 20 patients, a conversion to a negative CMV PCR signal was observed during ganciclovir therapy. Two patients remained CMV PCR positive despite change of antiviral therapy to foscarnet. Out of these 21 patients, 11 are still alive and 10 have died. Death was due to leukemia relapse in 4 patients, generalized toxoplasmosis in 1 patient, and refractory graft-versus-host disease and pneumonia in 5 patients. In 2 of these 5 patients, CMV PCR was positive in the BAL fluid corresponding to CMV pneumonia, and these patients died due to respiratory failure despite mechanical ventilation. Regarding toxicities, we observed similar results to those described by Ljungman et al.[1] Only one patient experienced a renal toxicity defined as a rise in serum creatinine of at least 2-fold using the above-mentioned probenecid and prehydration.

From these data, we conclude that cidofovir is not a useful alternative to ganciclovir or foscarnet as a first-line CMV preemptive therapy. This conclusion contradicts Ljungman et al's conclusion.[1] Failure to respond to cidofovir might be due to an insufficient dosage or an incorrect time schedule. As only 5 patients did not respond to the initial therapy given cidofovir once a week, it might be more effective to give cidofovir once a week for a longer period of time. This is supported by the low toxicity rate observed in our patients, as well in the retrospective analysis by Ljungman. On the other hand, it is important to note that we treated 2 additional patients not responding to ganciclovir as a single agent because of a U97L mutation[3] known as ganciclovir resistance with the combination of ganciclovir and cidofovir. Both patients became CMV PCR negative after 3 weeks of combination therapy and remained negative for more than 3 weeks after treatment discontinuation. Thus cidofovir can be given with a low risk of toxicity even in combination with ganciclovir. In conclusion, the favorable toxicity profile of cidofovir should be considered in order to design a clinical study to define the optimal dosage and time schedule of cidofovir for CMV infection in allogeneic stem cell transplant recipients.

Table 1. Patient characteristics

Underlying disease	Donor type	PBSCs (17)	CMV status recipient/donor
AML (9)	Matched unrelated (11)	BM (5)	+/+ (11)
ALL (8)	Mismatched unrelated (5)	PBSCs (17)	+/− (6)
CML (2)	Matched related (4)	—	−/+ (4)
MDS (2)	Mismatched related (1)	—	−/− (0)

The number of patients with each characteristic is in parentheses. The median patient age was 43 years; the range was 19 years to 53 years.

AML indicates acute myeloid leukemia; ALL, acute lymphoblastic leukemia; CML, chronic myeloid leukemia; MDS, myelodysplasia; BM, bone marrow; PBSCs, peripheral blood stem cells.

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