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Polymerase chain reaction-based "pre-emptive" therapy with cidofovir for cytomegalovirus reactivation in allogeneic hematopoietic stem cells transplantation recipients: a prospective study

We prospectively evaluated the efficacy of the antiviral drug, cidofovir, as a pre-emptive therapy for cytomegalovirus (CMV) infection after hematopoietic stem cell transplantation. Cidofovir was effective in 57% of cases without significant toxicity; response was inversely related to CMV DNA copy number at diagnosis. Cidofovir may represent a first-line therapy with some advantages over other commonly used drugs.

Cytomegalovirus (CMV) infection remains the most frequent infectious complication after allogeneic hematopoietic stem cell transplantation (HSCT).[1] Pre-emptive therapy with ganciclovir and foscavir, especially if based on quantitative polymerase chain reaction (PCR) assays, reduces the risk of progression to CMV disease;[2,3] however, ganciclovir-induced neutropenia represents an independent risk factor for mortality,[4] while foscarnet causes renal toxicity.[5]

The nucleotide analog cidofovir has recently been licensed for treatment of CMV retinitis in patients with acquired immune-deficiency syndrome (AIDS); it is also active on adenoviruses and polyomaviruses, and its pharmacokinetic profile allows a once-a-week administration.[6] To evaluate the efficacy of cidofovir as a PCR-based pre-emptive therapy in HSCT recipients, we enrolled 56 consecutive patients in a prospective study; in 14 of these who showed CMV reactivation, therapy with cidofovir was instituted. The PCR assays for CMV DNA in plasma and whole blood samples were performed with a commercially available kit (CMV-Ibridoquant Kit; Bioline Diag., Turin, Italy), twice weekly from day +15 to +30, then weekly up to day +120. Patients positive (CMV genome copy number ≥100/mL of blood and ≥500/mL of plasma) in two consecutive assays received cidofovir as first-line pre-emptive therapy, with a shift to ganciclovir ± foscavir in case of therapy failure. Cidofovir was administered at a dose of 5 mg/kg weekly for two weeks followed by two doses (3 mg/kg) every other week. Patients received oral probenecid (2 g three hours before therapy, and 1 g two and eight hours after the end of the cidofovir infusion) and pre-hydration (2,000 mL); creatinine levels and proteinuria were monitored weekly. No other antiviral therapy was allowed concurrently with cidofovir, while all patients had received prophylaxis with intravenous acyclovir (500 mg/m^2/three times a day from day –5 to day +30).

The outcome of cidofovir therapy was defined as: *response*, negativization of PCR test; *failure*, persistence of PCR positivity after 2 doses, or progression after any dose of cidofovir as shown by an increase in DNA blood levels or a positive test for CMV pp65; *toxicity*, a >1.5-fold increase in serum creatinine levels or development of proteinuria.

Reactivation of CMV occurred in 14/56 patients at a median of 46 days (range, 21-97) after HSCT; in all cases it was associated with pancytopenia and in 6 with acute graft-versus-host disease (grade II-III) under steroid treatment (Table 1). Virus clearance was obtained in 8/14 patients (57%), in half of whom after two doses of cidofovir; all became pp65 negative. Table 2, which reports the percentage changes in DNA copy number along with treatment, shows that an almost complete clearance was obtained after the second dose. The mean number of CMV DNA copies in plasma at diagnosis was lower in responders

Table 1. Characteristics of the 14 patients who entered the study.

Age median (range,years)	41 (24-59)
Time from HSCT to CMV reactivation (days)	46 (21-97)
Diagnosis	
Acute myeloid leukemia	7
Acute lymphoid leukemia	2
Chronic myeloid leukemia	3
Multiple myeloma	2
Donor type	
HLA-identical sibling	9
Matched unrelated	4
Partially-matched (4/6) cord blood	1
Conditioning regimen	
TBI + Cy	9
CT	
CMV status of donor (D) and recipient (R)	5
D-/R+	3
D+/R+	11
Pancytopenia	14
Acute graft-versus-host disease	6

TBI, hyperfractioned total body irradiation (1320 cGy); Cy, cyclophosphamide; CT, other chemotherapy-only regimens. Pancytopenia= neutrophils < 10^9/L and/or platelets < 50×10^{12}/L.

Table 2. Changes in CMV DNA copy numbers during cidofovir treatment in the 8 patients who responded to the treatment.

CMV DNA copies (percent reduction after)	Blood	Plasma
First dose	53±22%	2±1
Second dose	79±19%	93±3
Third dose*	97±3%	99±1

*Values reported are expressed as the percent reduction (± SD) taking the value recorded at diagnosis, just before starting cidofovir treatment, as 100%.
Only 3 patients received a fourth dose.

(9,158 vs 188,815 DNA copies/mL, *p*=0.038, Mann-Whitney test) with a similar trend also for blood (6,307 vs 9,440 DNA copies/mL; *p*=0.070). Patients who failed to respond to cidofovir were treated with ganciclovir ± foscavir; however, three patients died, two because of CMV-related interstitial pneumonia, and one because of thrombotic thrombocytopenic purpura. Cidofovir treatment was well tolerated, and neither renal nor hematopoietic toxicity was observed.

In a recent report from the *Infectious Disease Working Party of the EBMT*,[7] cidofovir was shown to be effective in both primary and secondary pre-emptive therapy. In that study, 10/20 patients with CMV disease responded to cidofovir, as did 25/38 (66%) who had failed to respond to or relapsed after pre-emptive therapy with other agents; furthermore, 62% of patients receiving CDV as primary pre-emptive therapy responded. Cidofovir has also been employed as pre-emptive therapy in a pilot study in 4 patients[8] and in 10 patients after dose-reduced conditioning.[9] Our data are in line with results from the above studies, having obtained a 57% response; we also observed that response to cidofovir was influenced by viral load at diagnosis, and that after only two doses a complete virus clearance was obtained in half of responders. No renal toxicity developed, unlike in the retrospective EBMT analysis (25.6% of cases, being persistent in 57.1%); however, in this series, most patients had received previously, or concomitantly with cidofovir, other antiviral agents; indeed the frequency of renal toxicity decreased from 35% to 29% to 12% in patients who received cidofovir for CMV disease, or for secondary or primary pre-emptive therapy, respectively.

In conclusion, the results of this prospective study indicate that cidofovir may be safely and effectively used as a first choice pre-emptive treatment in HSCT recipients, especially in those with a low CMV load according to a PCR assay. Most importantly, early administration of cidofovir as the only antiviral agent is not complicated by renal toxicity. Cidofovir may be delivered in an outpatient setting, being better accepted by the patient and also more cost-effective.

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Acute myeloid leukemia in the elderly: evaluation of overall survival in 69 consecutive patients

The aim of this study was to evaluate the impact of an intensive induction treatment on overall survival in elderly patients (age ≥ 66 years) with acute myeloid leukemia (AML) observed in our institution. Although complete remission was achieved in 58% of treated patients, the median overall survival was equally poor for treated (n=26) and untreated (n=40) patients (5 and 2 months, respectively), raising the question about the usefulness of an aggressive treatment in elderly patients with non-M3 AML.

Acute myeloid leukemia in elderly patients is associated with a poor overall survival (OS), regardless of treatment. Possible explanations for this include the frequent evolution from an underlying myelodysplastic syndrome (MDS), a high frequency of unfavourable cytogenetic abnormalities, a poor performance status (PS) and/or the presence of associated diseases contraindicating intensive induction regimens.[1] In addition, when complete remission (CR) can be achieved, leukemia relapse occurs after a short time in the majority of cases.[2]

Between February 1986 and December 1995, 69 consecutive AML patients aged ≥66 years (median age 72, range 66-92 years; males 39, females 30) were observed in our institution. According to FAB classification the number in each group was M0 5, M1 5, M2 15, M3 3, M4 16, M5 8, M6 2, M7 2. Thirteen cases could be confidently considered as secondary AML (evolution of MDS).

Only 26 patients (38%; 12 males, 14 females, median age 68 years, range 66-74; M0 4, M1 5, M2 6, M4 7, M5 3, M7 1) in good PS (> 70%) and without evidence of secondary leukemia were treated with aggressive chemotherapy, consisting of 3 courses of induction therapy followed by monthly maintenance chemother-