CMV Management with Specific Immunoglobulins: A Multicentric Retrospective Analysis on 92 Allotransplanted Patients

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Abstract. CMV represents one of the most severe life-threatening complications of allogeneic stem cell transplantation (allo-SCT). Pre-emptive treatment is highly effective, but toxicity and repetitive reactivation of CMV represent a significant challenge in the clinical practice. The use of anti-CMV specific immunoglobulins (Megalotect) is controversial.

We retrospectively collected data on 92 patients submitted to allo-SCT for hematological malignancies, in whom Megalotect was used either for prophylaxis (n=14) or with pre-emptive therapy, together with an anti-CMV specific drug (n=78). All the patients were considered at high-risk, due to the presence of at least one risk factor for CMV reactivation.

The treatment was well tolerated, with no reported infusion reactions, nor other adverse events, none of the 14 cases treated with Megalotect as prophylaxis developed CMV reactivation. 51/78 (65%) patients who received Megalotect during pre-emptive treatment achieved complete clearance of CMV viremia, and 14/51 patients (29%) developed a breakthrough CMV infection. 7/78 patients (9%) developed CMV disease. The projected 1-year OS, 1-year TRM, and 1-year RR is 74%, 15%, and 19%, respectively. No differences were observed in terms of OS, TRM, and RR by comparing patients who achieved a complete response after treatment versus those who did not.

These retrospective data suggest that Megalotect is safe and well-tolerated. When used as prophylaxis, no CMV reactivation was recorded. Further prospective trials are warranted to identify the best set of patients who can benefit from Megalotect alone or in addition to anti-CMV specific drugs.

Keywords: CMV infection, CMV disease, Pre-emptive treatment, Prophylaxis.

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Introduction. Cytomegalovirus (CMV) infection still represent one of the major complications in the setting of allogeneic stem cell transplantation (allo-SCT), particularly when the immunological reconstitution is delayed or incomplete like in haploidentical or cord-blood transplantation. It can cause multi-organ disease in recipients of SCT, including pneumonia, hepatitis, gastroenteritis, retinitis, and encephalitis, and the disease can develop both early and later after the transplant procedure.

Reactivation of CMV can be observed in about 30 to 50% of the patients, depending on risk factors such as donor/recipient serology, development of graft versus host disease (GVHD), type of donor, level of donor/recipient matching and recipient's age. Moreover, any level of viremia is associated with impaired outcome after allo-SCT, mainly if infections develops early after transplant. Considering the increase of allo-SCT with post-transplant cyclophosphamid as GVHD prophylaxis in the last decade, this scenario is changing: various groups registered a high rate of viral infections in the early period, with a satisfactory infectious profile in long-term follow-up thanks to a rapid and robust immune-reconstitution.

In the past years, several trials explored the role of prophylaxis in reducing the incidence of CMV infection in allotransplanted patients. Gancyclovir has been demonstrated to be effective in reducing the incidence of CMV reactivation, CMV disease, and the use of pre-emptive therapy, but not overall mortality. Moreover, the toxic profile of gancyclovir, namely represented by severe neutropenia, hampered the extensive use of this drug for prophylaxis. Recently, letermovir has been demonstrated to be highly effective in reducing the incidence of clinically significant CMV infection and overall mortality, together with a very safe profile.

Gancyclovir, valganciclovir, foscarnet, and cidofovir have been widely used for pre-emptive therapy, guided by the monitoring of CMV DNAemia in plasma and, more recently, whole blood. This approach induces complete viral clearance in up to 70% of the cases, and this has dramatically reduced the incidence of one of the most dangerous complications after transplant, represented by CMV disease, that now can be seen in less than 10% of allotransplanted patients. Nevertheless, the routinely use of pre-emptive therapy is associated with evident toxicity in terms of neutropenia for gancyclovir and valganciclovir and renal impairment for foscarnet and cidofovir and, moreover, with the emergence of gancyclovir-resistant strains. As a consequence, each Clinician who manages CMV after allo-SCT aims to reduce the cumulative dose of anti-CMV specific drugs, in order to limit their toxicity.

Intravenous immunoglobulins (IV-Ig) have been proposed as potentially useful either in prophylaxis or in the pre-emptive setting against CMV. Even though some recently data in the pediatric population showed that IV-Ig significantly reduced the incidence of CMV infections and a recently published meta-analysis showed that the prophylactic use of IV-Ig reduced CMV disease, the results of historical meta-analysis did not lead to similar conclusions, and currently the routinely use of IV-Ig for CMV prophylaxis is not recommended. Anti-CMV Ig (Megalotect) is a specific Ig, which inhibits the entrance of CMV in the host cells. Moreover, it can neutralize viral particles, aid in complement-mediated lysis of viral particles, promote opsonization and phagocytosis, enhance antibody-dependent cellular cytolysis (ADCC), and enhance complement-mediated cytolysis. Even though these mechanisms of action are well established, few data are available concerning the role of Megalotect in CMV management, and published data are mainly on solid organ transplantation. Moreover, in the setting of allo-SCT, most of the published data come from the old single-center trial or recently published retrospective small series of patients.

Thus, we planned this retrospective multi-center study and collected the data on 92 allotransplanted patients, who received at least one dose of Megalotect either for prophylaxis or during pre-emptive therapy together with an anti-CMV specific drug.

Materials and Methods. We retrospectively collected the data on 92 patients submitted to allo-SCT in 6 Italian Bone Marrow Transplant Units between 2016 and 2017, who received at least one dose of Megalotect, either for prophylaxis or during pre-emptive therapy. In the two years of data collection, 539 patients have been consecutively allotransplanted in those Centers, and 242 (45%) developed at least one CMV reactivation.

Local databases and clinical charts were used for data collection, and selected queries were addressed on missing data. The allo-SCT platforms, in terms of conditioning regimens, GVHD prophylaxis and antimiobial prophylaxis, were based on local guidelines and protocols, upon written informed consent for transplant procedures and the use of medical records for research. This study is retrospective. No Ethical Committee approval has been
requested. All the transplanted patients for whom data have been collected have regularly signed the EBMT informed consent for transplant data collection which is requested for European PROMISE database. The clinical and biological data collected for this paper are those routinely assessed for every transplanted patient. CMV DNA-emia was monitored by RT-qPCR on either plasma or whole blood, according to single Center policy. In the vast majority of patients (90%), quantification of CMV DNA was made using the Q-CMV Real-Time Complete Kit (ELITechGroup S.p.A) as previously published. The response after pre-emptive treatment has been retrospectively evaluated at the time of the first CMV negative PCR from the start of pre-emptive therapy.

**Statistical Analysis.** Categorical variables were described as frequencies and continuous variables as median value. Overall survival (OS) was defined as the interval from allo-SCT to death, whatever the cause, and patients were censored at the date of the last contact if alive. Cumulative incidences were estimated for acute GVHD, transplant-related mortality (TRM), and relapse to accommodate competing risks. Relapse or progression was a competing risk for TRM; death from any cause was a competing risk for relapse. Relapse/progression and death from any causes were competing for risks for GVHD. The probabilities of overall survival (OS), progression-free survival (PFS) and GVHD and relapse-free survival (GRFS) were estimated using the Kaplan-Meyer estimator. All statistical analyses were performed with R (R Development Core Team, Vienna, Austria) software package.

**Results.** This report focuses on a series of 92 allotransplanted patients who received Megalotect either for prophylaxis (n=14 - 15%) or during first-line pre-emptive therapy, together with an anti-CMV specific drug (n=78 - 85%).

The clinical and transplant characteristics of the 14 patients who received Megalotect in prophylaxis are reported in Table 1a. It should be noticed that 2/14 cases (14%) were CMV negative. These cases received Megalotect in prophylaxis because of the haploidentical donor. The clinical and transplant characteristics of the 78 patients who received Megalotect with an anti-CMV specific drug (pre-emptive setting) are reported in Table 1b. Briefly, the median age of our patients’ population was 47 years (range 0 – 69). 6/78 patients (8%) were below the age of 14 years. The great majority of the patients were transplanted for acute leukemia (64/78 – 82%), in complete remission (60/78 cases – 77%), with a myeloablative conditioning regimen (56/78 – 72%) and from a matched unrelated donor (36/78 – 46%). The donor was haploidentical for 30/78 patients (39%). Interestingly, 74/78 patients (95%) were CMV IgG positive before allo-SCT. Four patients were CMV negative, and they all received a haploidentical donor. The rationale for Megalotect use in these cases was related to the high risk of developing CMV infection and disease because of the nonidentical donor. All but nine patients received an un-manipulated T-cell replete graft. Conventional anti-thymocyte globulin in combination with cyclosporine and a short course of methotrexate with or without mycophenolate was the most commonly used prophylaxis (50/78 cases; 64%).

Megalotect was well tolerated, and no infusion-related adverse reactions were observed. The details on Megalotect dose and schedule and CMV reactivation in the two settings of patients are reported in Table 2a and 2b. Briefly, focusing on the 14 patients (15%) who received Megalotect as prophylaxis, the median dose of Megalotect was 50 UI/Kg (range 50-100). Prophylaxis started at day -7 until engraftment. Respectively, 21% (n=3), 36% (n=5) and 43% (n=6) of these patients received Megalotect on a weekly, every two weeks, and every three weeks schedule. The median number of administrations was 2 (range 1-9). None of these patients developed CMV reactivation by day +100 (Table 2a).

Moving to the 78 patients (85%) who received Megalotect during first-line pre-emptive therapy, the median time from allo-SCT to CMV reactivation was 29 days (range -9 - +399), 73/78 patients (94%) reactivated CMV from day 0 to day +100 from allo-SCT. The median dose of Megalotect was 50 UI/Kg (range 10-100). Respectively, 62% (n=48) and 27% (n=21) of these patients received Megalotect on a weekly and every two weeks schedule. The median number of administrations was 3 (range 1-33). The first dose of Megalotect was administered within five days from the start of pre-emptive treatment. The anti-CMV specific drug used as pre-emptive therapy was gancyclovir in 33 cases (42%), foscarnet in 26 cases (33%), valganciclovir in 16 cases (20%) and two-drugs combination in 3 cases (3%). After a median of 20 days of therapy (range 3 – 190), 51 out of 78 patients (65%) achieved complete clearance of CMV viremia with Megalotect and first-line standard anti-CMV drug. 16/78 patients (20%) received pre-emptive therapy for more than four weeks, as maintenance. In 14/51 patients (29%), a breakthrough CMV infection was observed, and this was treated with second-line anti-CMV drugs only, without Megalotect. More detailed data on the breakthrough infection have been obtained in 12/14 cases. In these cases, the breakthrough CMV infection occurred after a median of 30 days (range 7 – 60) from CMV negativity obtained with first-line pre-emptive therapy with anti-CMV specific drug and Megalotect. In all the cases the breakthrough CMV infection occurred after Megalotect discontinuation.
Table 1a. Population characteristics for prophylaxis treatment.

| Variable | Population (N= 14) |
|----------|--------------------|
| Median follow-up, months, (range) | 14 (12-47) |
| Patient median age (range) | 45 (20-65) |
| Disease, n (%) | | |
| AL | 12 (86%) |
| Lymphoma or MM | 2 (14%) |
| Disease status, n (%) | | |
| CR1 | 8 (57%) |
| CR>1 | 2 (14%) |
| Advanced | 4 (29%) |
| Donor, n (%) | | |
| MRD | 2 (14%) |
| MUD | 7 (50%) |
| Haploidentical | 3 (22%) |
| CBU | 2 (14%) |
| Recipient CMV status, n (%) | | |
| Positive | 12 (86%) |
| Negative | 2 (14%) |
| Donor CMV status, n (%) | | |
| Positive | 2 (14%) |
| Negative | 12 (86%) |
| Recipient/donor CMV status, n (%) | | |
| Neg/neg | 1 (7%) |
| Neg/pos | 1 (7%) |
| Pos/neg | 11 (79%) |
| Pos/pos | 1 (7%) |
| Conditioning intensity, n (%) | | |
| RIC | 0 |
| MAC | 14 (100%) |
| Stem cell source, n (%) | | |
| PB | 12 (86%) |
| BM | 0 |
| CBU | 2 (14%) |
| Main GvHD-prophylaxis platform, n (%) | | |
| T-repleted, ATG-based | 4 (29%) |
| T-repleted, PTCy-based | 1 (7%) |
| T-repleted, other | 9 (64%) |
| Details: | | |
| ATG – CSA+MTX±MMF | 4 (29%) |
| PTCy – CSA+MMF | 1 (7%) |
| Sirol+MMF | 9 (64%) |

Seven out of 78 patients (9%) developed CMV disease, with gut and lung localization in 5 and 2 cases, respectively. In 2/7 cases (40%), CMV disease was recorded after the failure of first-line anti-CMV treatment. Thus, 7% of the patients (2/27) who did not achieve CR after first-line pre-emptive therapy developed CMV disease. The median time from allo-SCT to CMV disease was 35 days (range 9 – 281), the median time from first CMV reactivation to CMV disease was 31 days (range 2 – 270), and 4/7 cases (57%) developed CMV disease early during the first CMV reactivation. All these cases of CMV disease were managed with anti-CMV specific drugs (gancyclovir in 2 cases, foscarnet in 3 cases and combination of the two drugs in 2 cases) with IV-Ig as suggested by data from metanalysis. 19

Overall, the cumulative incidence of grades II-IV and III-IV aGVHD at 100 days was 38% (95% CI 28-48) and 10% (95% CI 5-17), respectively (Table 3). The incidence of moderate-severe chronic GVHD was

Table 1b. Population characteristics for pre-emptive treatment.

| Variable | Population (N= 78) |
|----------|--------------------|
| Median follow-up, months, (range) | 12 (2-49) |
| Patient median age (range) | 47 (0-69) |
| Disease, n (%) | | |
| AL | 64 (82%) |
| Lymphoma or MM | 6 (8%) |
| MPN | 6 (8%) |
| Other | 2 (2%) |
| Disease status, n (%) | | |
| CR1 | 37 (47%) |
| CR>1 | 23 (30%) |
| Advanced | 18 (23%) |
| Donor, n (%) | | |
| MRD | 12 (15%) |
| MUD | 36 (46%) |
| Haploidentical | 30 (39%) |
| Recipient CMV status, n (%) | | |
| Positive | 74 (95%) |
| Negative | 4 (5%) |
| Donor CMV status, n (%) | | |
| Positive | 43 (55%) |
| Negative | 34 (44%) |
| Unknown | 1 (1%) |
| Recipient/donor CMV status, n (%) | | |
| Neg/neg | 3 (4%) |
| Neg/pos | 1 (1%) |
| Pos/neg | 31 (41%) |
| Pos/pos | 42 (54%) |
| Conditioning intensity, n (%) | | |
| RIC | 22 (28%) |
| MAC | 56 (72%) |
| Stem cell source, n (%) | | |
| PB | 49 (63%) |
| BM | 29 (37%) |
| Main GvHD-prophylaxis platform, n (%) | | |
| T-repleted, ATG-based | 50 (64%) |
| T-repleted, PTCy-based | 13 (17%) |
| T-repleted, other | 9 (11%) |
| Ex-vivo T cell depletion | 6 (8%) |
| Details in T-repleted: | | |
| ATG – CSA+MTX±MMF | 50 |
| ATG alone | 3 |
| PTCy – CSA+MMF | 13 |
| CSA+MTX±MMF | 3 |
| Sirol-MMF | 3 |
| ATG dose, median (range) | | |
| Thymoglobuline (n= 35) | 25 mg/Kg (5-25) |
| Fresenius (n= 18) | 25 mg/Kg (20-30) |

Table legend: AL=acute leukemia; MM=Multiple Myeloma; CR=complete remission; MUD=Matched Unrelated Donor; CBU= Cord Blood Unit; MRD=Matched Related Donor; MAC=myeloablative Conditioning; RIC=Reduced Intensity Conditioning; BM=bone marrow; PBSC=Peripheral Blood Stem Cells; CSA=Cyclosporine; MTX=Methotrexate; ATG=Anti-tymocyte Ig; PTCy=Post-Transplant Ciclophosphamide; MMF=Micophenolate; Siro=Sirolimus.
Discussion. Although the mortality for CMV in allotransplanted patients has decreased significantly because of pre-emptive therapy, CMV still reactivates in 30% - 50% of allo-SCT recipients.1,2 CMV treatment has been optimized in allo-SCT recipients over the past decade, mainly when used preemptively, but several questions remain. Moreover, new treatment options for CMV are urgently needed because the currently available drugs have significant limitations.13

In this paper, we report the outcome of 92 hematological patients treated with allo-SCT in 6 Italian Transplant Centers, who received at least one dose of Megalotect either for prophylaxis (n=14) or during pre-emptive treatment (n=78). Even though these results derive from a retrospective analysis, we observed that Megalotect was safe with no reported adverse reactions. In the prophylaxis setting, no CMV infections were observed. This result is of particular interest and, although it should be confirmed in prospective trials, it suggests that Megalotect by itself may help to control CMV infection. In fact, some in vitro studies suggest that the binding of Megalotect to the viral antigens may prevent the CMV binding to target cells, thus modulating CMV infection and disease, until anti-CMV CD8+ T-cells are present.30 It should be noticed that the dose, the schedule, and the number of administrations of Megalotect in the prophylaxis setting is widely variable in this series. This heterogeneity is due to the lack of published data and reflects the different Centers’ policy and internal guidelines for CMV management. Even though the introduction of letermovir for CMV prophylaxis in the first 100 days after allo-SCT is rapidly changing the scenario of CMV management, we think that 100 UI/Kg i.v. every two weeks from -7 to engraftment or eventually day +90 after allo-SCT could be the object of further prospective trials exploring the role of anti-CMV Ig in this setting.

Moreover, in the pre-emptive setting, 65% of the patients achieved complete CMV-clearance with first-line therapy and Megalotect after a median of 20 days (range 3 – 190). As observed for the prophylaxis setting, the wide range of anti-CMV pre-emptive treatment duration is atypical, and this reflects the different policies of the different centers in this field. 16/78 patients (20%) received pre-emptive therapy for more than four weeks, as maintenance. Moreover, it should be noticed that the time-point of CMV reactivation in these 78 cases varies widely concerning allo-SCT (from the day -9 to day +399). Most of the patients (73/78, 94%) reactivated CMV between day 0 and 100 days from allo-SCT. We decided to include in this report also the five patients who received Megalotect with an anti-CMV specific drug for a late CMV reactivation (mostly during GVHD), in order to have a “real-life” picture of the CMV management in the transplant Centers that participated to the study. We are aware that our results are in line with the response rate reported with conventional pre-emptive therapy with anti-CMV specific drugs alone, but it should be noticed that our patients represent a highly negatively selected cohort, in terms of risk of CMV reactivation. Thus, we can speculate that Megalotect may have played a role in inducing a fast and complete viral clearance in the majority of patients. We compared our
cohort of patients with a historical cohort of 122 patients transplanted from 2010 to 2017 in 2 of the six transplant Centers, who received pre-emptive therapy for CMV reactivation without Megalotect. We did not find any statistically significant difference in terms of response rate, duration of pre-emptive treatment, and breakthrough CMV infections. It should be noticed that, due to the evolution of the transplant approach in the last 20 years, these two populations were not well balanced with respect to the clinical and transplant characteristics and this is an extreme bias for drawing any conclusion (data not shown). Therefore, we believe that there is an urgent need for a prospective trial to better explore the role of Megalotect in CMV prevention and treatment.

Only 9% of the patients of the present series developed CMV disease, and none of the 24 deaths were related to CMV. We think that these data are of interest, considering that all the patients were at high risk of CMV infection and disease, mainly for unfavorable serology (R+) or haploidentical transplant or acute GVHD requiring treatment.

The role of anti-CMV Ig in the management of CMV in allotransplanted patients has been poorly explored in clinical trials, and currently, its use is not recommended in clinical practice. In 1998 Bacigalupo and Colleagues published the data of a randomized trial on 128 patients who received Megalotect versus conventional IV-Ig weekly from the day -7 to day +100. Antigenemia was used for CMV monitoring, and they found a trend for a reduced incidence of 1-year cumulative incidence of CMV antigenemia and grades II-IV acute GVHD in patients treated with hyper-immune anti-CMV Ig. Very recently Alsuliman and Colleagues published the results of a retrospective analysis on 23 patients who received Megalotect with or without anti-CMV specific drugs, mainly as salvage treatment. They observed a response rate of 87% after a median of 15 days of therapy, and the incidence of subsequent CMV reactivation was 22%. The optimal dose of anti-CMV Ig in these patients has to be better investigated. Some of the published papers report dosages much higher (100 – 200 UI/Kg/dose) than the ones reported in this analysis and usually administered for more than the median doses reported in our series. It should be noticed that the optimal dose and schedule of anti-CMV Ig has not been established yet, and the high variability reported in the few published papers probably reflects the different Centers' policy of CMV management. Of note, the dose of 50 UI/Kg administered in our patients was high enough to maintain a level of peripheral blood IgG greater than 500 mg/dl, which is considered associated with relatively high efficacy of the humoral immune system in controlling infections after allo-SCT. Further studies are warranted in order to address the optimal dose and schedule of Megalotect.

As previously stated, our data are retrospective, with several limitations that can derive from many aspects, including the changing of transplant scenario, the evolution of pre-emptive strategy and CMV monitoring and the possible bias of positive or negative selection by Clinicians in the choice to administer Megalotect. As a consequence, prospective trials to explore the role of Megalotect in prophylaxis and pre-emptive settings are strongly warranted in high-risk patients. In this latter group, the major issue is to assess if a combination of anti-CMV specific drugs and Megalotect may reduce the days of pre-emptive therapy and thus the toxicity, and to verify if the combination can reduce the incidence of breakthrough CMV infection.

The future management of CMV infection is expected to change rapidly, due to the availability in clinical practice of the new anti-CMV drugs, namely letermovir, recently licensed in the United States and Europe for the prophylaxis of CMV in the first 100 days after transplant. The use of this drug will probably reduce the incidence of early CMV reactivation, but we will have to manage late-onset CMV reactivations, which are expected in about one-third of the patients who will receive letermovir for prophylaxis. It may be interesting to prospectively explore the role of Megalotect in preventing this event too.

References:

1. Stacyczynski J, Who Is the Patient at Risk of CMV Recurrence: A Review of the Current Scientific Evidence with a Focus on Hematopoietic Cell Transplantation. Infect Dis Ther. 2018;7(1):1-16. https://doi.org/10.1007/s40121-017-0180-z PMid:29204910 PMCid:PMC5840099
2. Pollack M, Heugel J, Xie H, Leisenring W, Storek J, Young JA, Kukreja M, Gress R, Tomblyn M, Boeckh M. An international comparison of current strategies to prevent herpesvirus and fungal infections in hematopoietic cell transplant recipients. Biol Blood Marrow Transplant. 2011;17:664-673. https://doi.org/10.1016/j.bmmt.2010.07.026 PMid:20699126 PMCid:PMC3358229
3. Aversa F, Prezioso L, Manfra I, Galaverna F, Spolzino A, Monti A. Immunity to Infections after Haploidentical Hematopoietic Stem Cell Transplantation. Mediterr J Hematol Infect Dis. 2016 Oct 25;8(1):e2016057. eCollection 2016. https://doi.org/10.4084/mjhid.2016.057 PMid:27872737 PMCid:PMC5111540
4. Montoro, J., & Sanz, J. (2016). Infectious Complications After Umbilical Cord-Blood Transplantation From Unrelated Donors. Mediterr J Hematol Infect Dis, 8, e2016051. https://doi.org/10.4084/mjhid.2016.051 PMid:27872731 PMCid:PMC5111540
5. Boeckh M, Leisenring W, Riddell SR, Bowden RA, Huang ML, Myerson D, Stevens-Ayers T, Flowers ME, Cunningham T, Corey L. Late cytomegalovirus disease and mortality in recipients of allogeneic hematopoietic stem cell transplants: importance of viral load and T-cell immunity. Blood. 2003;101:407-414. https://doi.org/10.1182/blood-2002-03-0993 PMid:12393659
