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The Bottom Line

CMV and Relapse: What Has Conditioning to Do with It?

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Manjappa and colleagues confirmed in the present study reports by us and others that a cytomegalovirus (CMV) reactivation is associated with a significant relapse risk reduction in patients with acute myeloid leukemia (AML) after allogeneic stem cell transplantation (SCT) with myeloablative conditioning (MA) [1-3]. This finding challenged fundamentally our established perceptions toward CMV reactivation after SCT. This knowledge evokes, besides amazement, the insight that we know little about the sophisticated immunological processes interacting between leukemia and a donor-derived immune system that is challenged by a CMV infection. However, it is of great interest to understand the mechanism by which CMV reactivation increases such an observed antileukemic effect in AML.

Green and colleagues [2] showed in a large cohort study that a decreased relapse risk after CMV reactivation was detectable only in AML at day 100 after transplant, but not in other diseases such as chronic myeloid leukemia, acute lymphoblastic leukemia, or lymphoma. These results differed from those published by Ito and colleagues [4], who observed that CMV reactivation was associated with a decreased relapse in a cohort of 110 patients with chronic myeloid leukemia. Green and colleagues argued that the great majority of patients in the Ito study received ex vivo T- cell–depleted grafts, which typically results in a robust natural killer (NK) cell reconstitution after transplant.

In contrast to these results, Thomson et al. [5] found no association between CMV reactivation and relapse risk in 100 patients with AML who received alemtuzumab, which depletes a variety of immune cells, including NK cells, and persists in vivo for prolonged periods. Their results are in line with our results of a retrospective study showing that patients with AML (n = 64) after myeloablative T cell–depleted transplantation using alemtuzumab did not benefit from a CMV reactivation. Although alemtuzumab completely abolished the CMV induced antileukemic effect in our study, antithymocyte globulin (ATG) may have only a moderate influence on it according to our observations in a different cohort of 100 AML patients transplanted from HLA-mismatched unrelated and sibling donors after using a myeloablative conditioning regimen (unpublished observation). The reason for that might be that ATG worsens only the reconstitution of CD4 T cells but not of NK and CD8 T cells, which might play a role in the CMV-mediated antileukemic effect [6]. Thus, Scheper and colleagues [7] reported that gamma/delta T cells elicited by CMV reactivation after allo-SCT cross-recognize CMV and leukemia. They supposed that this T cell population contributed to the CMV-induced antileukemic effect. Foley et al. [8] demonstrated increased populations of interferon-γ producing NKG2C1 and NKG2A2 NK cells in SCT recipients as soon as 2 weeks after CMV viremia was detected. In addition to T cells, NK cells possess remarkable antileukemic affects against AML in the transplant setting [9].

But what is the role of a conditioning regimen in this context? Manjappa and colleagues [1] reported that the antileukemic effect of a CMV reactivation was only found in patients receiving MA conditioning (n = 206) but not in patients who received reduced-intensity conditioning (RIC; n = 58). What is different about RIC compared with MA conditioning for the CMV-induced antileukemic effect? In their smaller RIC cohort, 44 of 58 patients received ATG as part of their conditioning regimen and a higher proportion of patients were in first complete remission (60%) than in the MA cohort (44%). Manjappa and colleagues argued that in vivo T cell depletion by ATG in the RIC cohort may result in mitigating the enhanced graft-versus-leukemic effect induced by CMV reactivation, which underlines the importance of graft-derived T cells in mediating this effect. Furthermore, they argued that host-derived memory T cells can persist for up to 6 months in RIC patients and contribute toward immunity against CMV [1].

Persisting host T cells could contribute to clearing of CMV upon its reactivation, thereby possibly preventing optimal donor T cell and NK cell activation that cross-reacts toward AML. It is unclear, however, whether these differences explain the distinct mechanism or simply reflect other variables, including a small sample size with insufficient statistical power. On the other hand, it is true that most patients in the study by Green et al. [2] and in our study [3] received MA conditioning, which supports this thesis of Manjappa and colleagues.

Besides the great interest to learn the mechanism of the protective effect of CMV reactivation, it is finally of importance if and how we can clinically use this finding. Because it is not justified to change our CMV treatment strategy due to the higher therapy-associated mortality of a CMV reactivation after SCT, CMV vaccination might be an option to induce similar effects without increasing the rate of therapy-associated mortality. First results from a phase II study of a CMV vaccine showed a stimulation of specific immune responses to CMV [10]. Therefore, it remains to be seen if CMV vaccination might not only prevent CMV infections but also reduce the relapse risk of patients with AML. This might be possible if the CMV vaccine induced

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stimulation of specific immune responses to CMV in patients with AML after SCT is potent enough. However, this effect cannot be expected from new antiviral drugs towards CMV discussed elsewhere.

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Optimal Autologous Peripheral Blood Progenitor Cell Mobilization Involves More Than the CD34+Yield

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Peripheral blood progenitor cell (PBPC) mobilization is the first step in the autologous stem cell transplant (ASCT) procedure. The regimen used for PBPC mobilization affects not just the cost of ASCT but also the patient's total transplant experience. We often focus on the absolute numeric progenitor cell yield as measured by the CD34+ cell dose in the mobilized graft; however, the optimal mobilization strategy should be judged on more than this metric alone. The PBSC graft quantity and quality affects engraftment kinetics and, although controversial, may influence relapse-free survival, overall survival, and the development of post-transplant complications such as therapy-related myelodysplastic syndrome and acute myeloid leukemia (tMDS/AML) [1-3]. The choice of whether to mobilize patients using either granulocyte colony-stimulating factor (G-CSF) alone, G-CSF plus plerixafor, or chemotherapy plus G-CSF is usually based on the patient's disease status, prior therapy, predicted poor mobilizer status, transplant center protocol, cost considerations, and the individual patient situation. Chemotherapy plus G-CSF is generally viewed as an attractive strategy to achieve needed anti-tumor effect and to ensure at least an adequate (2×10^6/kg CD34+ cells) or a successful ($\geq 5 \times 10^6$/kg CD34+ cells) apheresis yield at a reasonable cost.

In this issue, Shin Young Hyun et al. [4] reports on the outcomes of mobilizing with high dose etoposide plus GCSF as compared to cyclophosphamide plus GCSF and platinum based salvage regimens plus GCSF. Etoposide plus GCSF is not a new mobilization regimen, however its utilization declined following concerns regarding the reported higher incidence of tMDS/AML following etoposide based mobilization and ASCT [3]. This is probably not so and there are reports indicating that the incidence of t(MDS/AML) after etoposide is not significantly increased [5–7]. The dose of etoposide utilized in this retrospective study by Shin Young Hyun et al. was 1.5g/m2. This dose is lower than the more conventional 2g/m2. It however appears to have led to an overall greater number of successful ($\geq 5 \times 10^6$/kg CD34+ cells) mobilizations at 86% compared to cyclophosphamide 4g/m2 plus GCSF and the platinum based regimens (ICE, DHAP and ESHAP) plus GCSF at 45% and 61% respectively (p=0.004). The success of this lower dose is in keeping with the observation by Kanfer et al., that reducing the dose of etoposide to 1.6g/m2 or 1.8g/m2 resulted in adequate and successful mobilizations compared to higher doses. An even lower dose of etoposide (0.75g/m2) was utilized with success in patients with multiple myeloma, some of whom were predicted poor mobilizers [8]. Consistent across all reports of high and intermediate dose etoposide based mobilization is the high incidence of neutropenic fever compared to growth factor based strategies where the incidence is zero. The incidence of 67% in this report is higher than previously reported rates that range from of 17 – 27%. This complication unfortunately increases the cost and inconvenience to patients due to the need for readmission for intravenous antibiotics. There is more myelosuppression and utilization of blood products with all chemo-mobilization based strategies; however in this report etoposide plus GCSF induced a significantly lower

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