Adenovirus Infections after Hematopoietic Stem Cell Transplantation: Still Unravelling the Story

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(See the article by Erard et al. on pages 958–65)

It was realized during the early history of hematopoietic stem cell transplantation (HSCT) that a major hindrance in improving outcome was posttransplant viral infections. Cytomegalovirus infection was identified early as a major cause of mortality, and the efforts invested in the understanding of the pathogenesis of cytomegalovirus disease and its prevention over the past 2 decades have had a significant impact in reducing deaths directly related to the virus. Discoveries involving Epstein-Barr virus–associated posttransplantation lymphoproliferation provided understanding, as well. These developments led to the emergence of other viral pathogens, such as adenoviruses, as major contributors to posttransplantation mortality.

Since 1960, adenovirus has been known to cause fatal infections in children with congenital immunodeficiency disorders [1]. However, it was not until 1985 that an attempt was made to understand the impact of this virus during the posttransplantation period [2]. A series of retrospective studies were performed over the subsequent 15 years that attempted to define post-HSCT adenovirus infection. It was perceived that adenovirus infection was, perhaps, more common in patients with graft-versus-host disease and in patients with a greater degree of immunosuppression. Yet, not much was understood about the pathogenesis of this infection or the reasons that some infected patients were asymptomatic and remained so whereas others succumbed to the same virus.

To attempt to address these issues, a prospective study by a group in the United Kingdom [3] and a subsequent study by a Dutch group [4, 5] were performed. In a retrospective and prospective analysis involving a small group of patients from the study populations of both groups [3–5], it was demonstrated that detection of adenovirus in peripheral blood samples by sensitive PCR assays predicts a fatal outcome. This study, indeed, had set the stage, and several studies in which quantitative PCR assays were used were subsequently performed [6]. In these studies, adenoviremia was detected during an asymptomatic stage when detected prospectively yet progressed in 2–3 weeks to disseminated and, often, fatal disease. Most of the patients studied underwent T cell depletion of the graft either in vivo or in vitro. Does adenoviremia, as detected by PCR assay, have a similar natural history of progression after unmanipulated grafts? The article by Erard et al. [7] in this issue of Clinical Infectious Diseases is another such attempt at further defining the significance of adenoviremia in patients receiving T cell–replete grafts.

The study by Erard et al. [7] highlights several interesting aspects of a retrospective analysis. The first study of adenovirus infection in HSCT recipients emerged from the Fred Hutchison Cancer Research Center (Seattle, WA), and it is, indeed, commendable that the investigators from the same institution have revisited the findings in the light of the current understanding of the pathogenesis of this infection. Archiving samples for future research is not strongly emphasized in clinical practice, often because of a combination of factors, such as lack of manpower and resources, regulatory issues, and, perhaps, lack of foresight regarding the impact such investigations could generate. Thus, critical retrospection is often as important as prospective studies.

What do we learn from the study by Erard et al. [7]? One might say that the findings are a repetition of what we already know from a number of other recent studies. Yet, despite all of the shortcomings, this study will have an impact on our overall understanding of post-HSCT adenovirus infection. The study design leaves little doubt regarding the comparability of the control and study groups with respect

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to variables, such as year, type, and conditioning of transplantation—the variables that often lead to the questioning of the viability of findings in retrospective studies. The weekly storage of plasma samples leaves little scope for speculation regarding the uniformity of assessment and the definitions used.

Erard et al. [7] documented that adenoviremia was detected several weeks (median, 3 weeks) before death in patients with fatal outcome attributable to adenovirus. This finding conforms to our current understanding of the natural history of adenovirus infection after HSCT. The virus probably reactivates from latency or progresses from low-grade persistence to a stage of viremia before it causes symptomatic dissemination and death [8]. Such sequential sampling elucidates the fact that increasing viral load, not simple viremia, is reflected by the highest DNA levels in patients with disseminated disease. Furthermore, these findings support redefining adenovirus disease on the basis of adenoviremia rather than on the basis of the test results of tissue biopsy samples alone. Clearly, early detection of critical or increasing adenoviral load is the trigger to act. This introduces the yet unresolved issue of “how to act.”

There are 3 issues involved in the treatment of adenovirus infection: who, when, and how to treat. When and for whom to initiate treatment (if we presume that there is a standard treatment for this infection) has been open to speculative debate for much of the past decade. However, the first prospective study to address this issue was published in 2002; shortly after this report, studies were performed by other groups demonstrating that progression of adenovirus disease is a function of the host immune response [9, 10]. Severe persistent lymphopenia leads to disease progression and death, whereas lymphocyte recovery, which is often associated with reduction or withdrawal of immunosuppression, can lead to recovery. This balance was postulated to be regulated by adenovirus-specific T cells. Indeed, in several recent studies, this was proven to be the case [11].

By the very nature of the transplantation, we can predict the group of patients who are at highest risk for infection, such as those receiving an extensively T cell-depleted graft, particularly from an unrelated or mismatched related donor and, particularly, children. Then, what about patients receiving T cell-replete grafts? Unfortunately, Erard et al. [7] did not address this point in their study. There would surely have been data on lymphocyte recovery in these patients that, perhaps, would be worth analysis. The most likely scenario of progressive adenovirus infection in recipients of T cell-replete grafts involves those receiving immunosuppressive treatment for graft-versus-host disease or any other condition. It is often difficult to reduce immunosuppression in this group of patients, and some patients would have received anti-T cell antibodies to treat graft-versus-host disease that was unresponsive to steroid therapy. Accepting this inadequacy in the study by Erard and colleagues, with the hope that this might be addressed in the future, I would retreat to the same algorithm proposed 5 years ago [8], in which the emphasis is to treat adenovirus infection preemptively on the basis of the current T cell count, potential for T cell recovery, and kinetics of adenoviremia. It is encouraging to note that detection of adenovirus-specific T cells might become more widely applicable [9]. Short of that, the surrogate markers, such as absolute lymphocyte count and CD4+ T cell recovery, will have to suffice.

Thus, if we think that we have, to some extent, sorted out the first 2 issues of who and when to treat, we are indeed faced with the most difficult challenge of all: how to treat adenovirus infection after HSCT. In the report by Erard et al. [7], this contentious subject was briefly examined. Antiviral therapy plays a prominent role in treating cytomegalovirus infection. However, the same is not true for adenovirus infection. Scattered reports of response to and failure of both ribavirin and cidofovir therapy have been featured in the literature over the past decade, without any randomized study. The lack of efficacy of ribavirin therapy in reducing adenovirus load in blood was well documented by Leiden et al. [12]. The effect of cidofovir therapy is less than definite, considering the prominent efficacy in vitro. The reports of successes are confounded by the lack of description of the immune recovery [13]. Failures of therapy have also been reported with equal zest [14]. Perhaps the best-documented recovery from adenoviremia was in relation to immune recovery [10, 11, 15]. The studies in which this subject is examined demonstrate a relationship between recovery or lack of recovery of adenovirus-specific T cells and a favorable or fatal outcome, respectively.

The findings of recent studies have raised the possibility of adenovirus-specific adoptive immunotherapy, and early clinical studies have confirmed the feasibility and safety of such an approach [16, 17]. Adenovirus-specific immune responses seem to be predominantly mediated by CD4+ T cells. Is that truly the case, or is it a skewing of response as a result of the antigen employed in vitro? Many such questions remain unanswered, but, hopefully, researchers are headed in the right direction.

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