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EDITORIAL COMMENT

Malignancy Post Heart Transplantation

No Free Lunch*

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Survival following cardiac transplantation has improved significantly with the advent of better immunosuppression therapy. In the current era, approximately 50% of patients survive more than 13 years, with an increasing population of patients surviving beyond 20 years (1). With the success of cardiac transplantation, older patients and those with comorbidities such as prior malignancy, diabetes, and renal insufficiency are now frequently treated with transplantation. This improvement in survival has subsequently increased the duration of immunosuppression therapy and, including the population of patients with significant co-morbidities, has resulted in the significant rise in de novo malignancies.

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In this issue of the *Journal*, Youn et al. (2) describe the temporal trends of de novo malignancies after heart transplantation by using a retrospective analysis of 17,587 adult heart transplant recipients from the International Society of Heart and Lung Transplant (ISHLT) registry from 2001 to 2011. More than 10% of heart transplant recipients developed a de novo malignancy 1 to 5 years post-transplantation. The overall cohort was also analyzed by time period, and the authors report an increase of 12.4% in de novo malignancies in the cohort treated between 2006 and 2011, compared to 10% in the cohort treated between 2000 and 2006; this resulted in an absolute increase of 2.4%. Most of this rise was attributed to an increase in skin cancer. There was a small increase in solid organ malignancy and essentially no change in what was a remarkably low incidence of post-transplantation lymphoproliferative disease (PTLD) (approximately 1%).

SKIN CANCER

The problem of skin cancer in organ transplant recipients has best been studied in renal studies, despite the fact that this disease represents a greater problem in thoracic organ recipients due to more intense immunosuppression regimens. Compared to the incidence of skin cancer in the general population, in heart transplant recipients, the incidence is approximately 65 to 250 times more frequent. More than 90% of cases are due to squamous and basal cell carcinomas. Unlike the general population where the incidence of basal cell carcinomas exceeds squamous cell cancers, the reverse is true in organ transplantation recipients. In heart transplant patients particularly, there is an exponential increase in squamous cell cancer and a linear increase in basal cell cancer. The former tends to be more aggressive, presents with more local recurrences, and has greater metastatic potential than in the general population (3-6). Factors contributing to the development of skin cancers include the duration and intensity of immunosuppression, the presence of human papilloma virus associated with warts that can transform into cancer, increasing age, male sex, white race, smoking, and sun exposure. Youn et al. (2) observed a similar increased risk of skin cancer in older, male heart transplant recipients and also those who received induction therapy. Association with the use of induction therapy may provide an important future strategy to limit the development of skin malignancies, as use of less aggressive immunosuppression regimens in selected heart transplant recipients at high risk for skin cancer could be advised. Although Youn et al. (2) describe a temporal increase in the incidence of skin cancers in the recent heart

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transplant cohort, it is important to emphasize that a temporal increase in skin cancer also is currently being observed in the general population, and it is likely that the same factors are contributing to both transplant and nontransplant patients alike.

Clearly, the mere presence of skin cancers increases morbidity, which is related to the need for excision of malignant lesions and more intense dermatologic surveillance. In this report, Youn et al. (2) emphasized the increased mortality in heart transplant patients with skin cancer versus those recipients without malignancies. Survival was compared between these groups beginning at the median time of skin cancer detection post-transplantation. This is quite surprising and may not be accurate. Despite the more aggressive nature of skin cancer post-transplantation, the mortality directly attributed to skin cancer has been remarkably low. In fact, Brewer et al. (4) describes in a single-center study of 312 heart transplantation recipients the high incidence of skin cancer (1,395 cancers) with a high recurrence rate but only 1 death attributable to skin cancer (malignant melanoma). In my own practice, where I have had the privilege of caring for more than 2,000 heart transplant recipients, although I have seen innumerable skin cancers, there were only 2 patients whose deaths could be directly linked to metastatic squamous cell skin cancer. Furthermore, the statistical analysis used in this study by Youn et al. (2) is inherently problematic. Cancer is an event that occurs post-transplantation and the influence of a diagnosis of cancer on subsequent post-transplantation mortality is best analyzed using Cox regression with cancer as a time-updated covariant. For the analysis to be better informed, the authors needed to be more selective in their control group. Clearly, the factors predisposing to skin cancer, such as increased age, smoking history, male sex, and diabetes, are all associated with decreased survival, and without the advantage of having propensity matching of this cohort, the conclusions may be flawed. Nevertheless, the issue of increasing frequency of skin cancer in transplantation patients is an important and underappreciated message that deserves to be delivered to the transplantation community.

SOLID ORGAN MALIGNANCIES

Unlike the large increase in skin cancers, solid organ malignancies had just a slight increase over time. Whether this increase is due to better reporting of adverse events or greater surveillance for malignancy in the recent era is unclear. Moreover, the data reported are incidence rates not normalized to the general population. Most studies have not compared incidence and type of solid tumor malignancies with their respective frequencies in the general population matched for age, sex, and race. One study from Columbia Presbyterian Medical Center did compare the development of de novo solid malignance in 851 adult patients, using Surveillance Epidemiology and End Results Registry (SEER) data (7). In that study, 8.6% of patients developed a de novo solid tumor. However, there was no increase in de novo solid malignancies compared to the general population for most common malignancies (breast, prostate, lung). Additionally, solid tumor malignancies associated with viral infections such as cervical cancer were more common in transplantation patients than in the general population.

Youn et al. (2) also showed diminished survival in those patients with nonskin solid tumors than in those without malignancies. Although the aforementioned flaws with the authors' survival analysis still applies, unlike skin malignancies, it is reasonable to assume that the development of many solid organ tumors are more likely to contribute substantially to patients in whom survival was worsened.

Interestingly, the incidence of post-transplantation lymphoproliferative disease was surprisingly low both in the early and the late cohort, at approximately 1% compared to what has previously been reported, from 3% to 9% (8). This is in sharp contrast to pediatric heart transplantation patients in whom PTLD remains a leading cause of malignancy post-transplantation. This low incidence may also reflect the fact that PTLD related to Epstein-Barr virus infection has a relatively early presentation, frequently within the first year post transplantation, and in this analysis, these patients were excluded. Whether this observed decrease in PTLD is due to change in immunosuppression, better infectious disease prevention and treatment, and/or under-reporting to the ISHLT registry remains unclear.

PREVENTION

Finally, are there any interventions that slow or reverse this trend in increasing malignancy rates post-transplantation? The obvious answer includes the development of more targeted immunosuppression in heart transplant candidates, and the authors are correct that patient-specific rather than protocol-driven immunosuppressive regimens should be considered and implemented more frequently. Avoidance of induction therapies in older recipient or in those with previous malignancy is another possible intervention. Newer immunosuppressive agents such as mTOR inhibitors should be considered as substitutes for calcineurin inhibitors in older patients at

high risk for malignancy or in patients with prior malignancies. Finally, better surveillance for development of malignancies needs to be discussed.

Our role as transplantation physicians is to assist our patients by monitoring for potential medical problems but, as survival post-transplantation continues to improve, no matter how vigilant we and our patients ultimately become, society must recognize and accept that, although we can alleviate one problem, we cannot solve them all. After all, there is a cost for long-term immunosuppression and allograft survival, and as we all know, "there is no such thing as a free lunch."

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