the sole imaging procedure, it would have missed additional small lytic skeletal lesions and diffuse spine involvement, which is readily detected by MRI.3,7 Another disadvantage of PET/CT is the false positive results especially in areas of inflammation or infection, deposits of brown fat, postsurgical changes, vertebroplasty changes, and occasionally other benign or malignant processes.8 In a prospective comparison among FDG-PET/CT, MRI, and conventional radiography, PET-CT was superior to plain radiographs, but, in 30% of patients, PET-CT scans of the spine and pelvis failed to show abnormal findings in areas in which MRI revealed an abnormal pattern of bone marrow involvement, more frequently of diffuse type. In contrast, in 35% of patients, PET-CT enabled the detection of myelomatous lesions in areas that were outside the field of MRI. By combining MRI of the spine-pelvis and PET-CT, the ability to detect sites of active multiple myeloma (MM), both medullary and extramedullary, was as high as 92%.

After autologous stem cell transplantation, 15 of 23 patients had negative PET-CT scans (including 13 with very good partial response or near CR), while only 8 had normal MRI.9 The results of the study by Bartel et al are important as they reveal PET/CT as a technique that could lead to individualized therapeutic decisions especially in patients who have residual disease detected only by this procedure. Furthermore, PET/CT is the procedure of choice when extramedullary involvement is suspected (ie, in patients with rising serum LDH). However, further studies are needed before the recommendation of using PET/CT as the standard tool in both diagnosis and follow-up of MM patients.

Conflict-of-interest disclosure: The authors declare no competing financial interests.

REFERENCES

Comment on Claviez et al, page 2060

Allotransplantation in pediatric HL

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In this issue of Blood, Claviez and colleagues report on the outcomes of 91 patients younger than 18 years of age who underwent an allogeneic bone marrow transplantation for HL between 1987 and 2005. The outcomes were reported to the European Group for Blood and Marrow Transplantation.1

Fifty-one patients received a reduced-intensity transplantation (primarily a fludarabine-based regimen) while 40 patients received a myeloablative conditioning regimen. The probability of progression-free survival at 2 and 5 years was 40% plus or minus 6% and 30% plus or minus 6%, respectively. Overall survival at 2 and 5 years was 54% plus or minus 6% and 41% plus or minus 6%, respectively. Although the relapse rate for patients receiving myeloablative conditioning was similar to that for patients receiving a reduced-intensity conditioning for the first 9 months after transplantation, subsequent relapses were more frequent in the group receiving reduced-intensity conditioning.

Before one examines the overall and subgroup analyses presented by the authors, the potential problems associated with the analysis of “registry” data need to be considered. Because the clinical history for an individual patient is not presented, it is not clear why a particular treatment was given to an individual patient. In this registry dataset, approximately 55% of patients received an allogeneic transplantation as their first transplantation. Currently, no guidelines for treating relapsed Hodgkin lymphoma (HL) recommend allogeneic transplantation as the initial transplantation.2 It would be interesting to know why investigators chose allogeneic transplantation over the more standard autologous transplantation. It would have been helpful if the authors had presented separate outcome data for patients who received an initial allogeneic transplantation and those who received an allogeneic transplantation after a failed autologous transplantation. The fact that more than half of the patients reported had nonstandard treatment limits the usefulness of this data.

In this paper, the authors compare the results of patients receiving myeloablative to reduced-intensity conditioning. The authors conclude that reduced-intensity conditioning is associated with similar nonrelapse mortality and a higher relapse rate. But, before considering whether differences in outcome among subgroups are relevant, one must ensure comparability of the analyzed groups.

Salvage chemotherapy followed by autologous stem cell transplantation is the standard of care for pediatric HL patients who present with advanced-stage disease and fail front-line therapy. Patients who received reduced-intensity conditioning were more likely to have received 4 or more salvage regimens (P = .001) and were more likely to have undergone an
unsuccessful previous autologous transplantation ($P < .001$), compared with patients receiving a myeloablative chemotherapy regimen. Even though chemotherapy sensitivity and disease status at transplantation were comparable, my impression is that the patients receiving reduced-intensity conditioning represent a group with a higher likelihood of dying from complications related to the transplantation and to relapse. Thus, I think the “evidence” that reduced-intensity conditioning is associated with a higher relapse rate compared with myeloablative conditioning is flawed and should not be given significant credence.

It is unlikely there will ever be a randomized study evaluating the role of either autologous or allogeneic transplantation for treating relapse or primary progression in pediatric patients with HL. There is a general consensus among pediatric oncologists that high-dose chemotherapy and autologous peripheral stem cell transplantation is effective treatment for patients with primary refractory HL and for patients with advanced-stage disease at presentation who experience a relapse. Currently there is no indication to use allogeneic transplantation as the first transplantation unless the patient’s stem cells cannot be mobilized. The article by Claviez et al provides important information that patients who relapse following an autologous transplantation still have the potential for cure following allogeneic stem cell transplantation. In our center, such patients are generally offered a reduced-intensity conditioning regimen in an effort to reduce the nonrelapse mortality. It is clear from this article that reduced-intensity conditioning is being used more frequently. Between 1987 and 2001, 36% of patients received reduced-intensity conditioning compared with 75% between 2001 and 2005.

Only a registry study could provide sufficient data to begin to evaluate the role of allogeneic transplantation in the treatment of pediatric patients with HL. However, in evaluating conclusions drawn from registry data, reported subgroups must be analyzed carefully to ensure that they are comparable. This study clearly shows that allogeneic transplantation following a failed autologous transplantation is feasible and potentially curative for pediatric patients with relapsed HL. However, the comparison between myeloablative and reduced-intensity conditioning is limited in value because the 2 groups have significantly different earlier treatment. It is likely that reduced-intensity conditioning will continue to increase in frequency.

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GENE THERAPY

Comment on Mingoazzi et al, page 2077

Muscling through AAV immunity

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AAV–1 is one of the most promising vectors for gene delivery to skeletal muscle. In this issue of Blood, Mingoazzi and colleagues now demonstrate that AAV–1–mediated gene transfer into human skeletal muscle results in activation of capsid-specific T cells.1

Evidence continues to accumulate demonstrating that gene therapy may be therapeutically effective in patients suffering from different types of hereditary diseases.2,3 These recent successes in gene therapy reflect, at least in part, continued improvements in gene delivery technologies. In particular, gene delivery vectors derived from the nonpathogenic adeno-associated virus (AAV) have been used to cure monogenic diseases in preclinical animal models and thus far have yielded some promising results in clinical trials. Despite these advances, the immune response toward the therapeutic protein or the gene–engineered cells themselves represents a potential hurdle that may prevent long-term therapeutic effects. Unfortunately, the assessment of immune responses following gene therapy in preclinical animal models does not always accurately predict the outcome in humans.3 Hence, it is extremely important to fully study the immune consequences of gene transfer in human subjects enrolled in clinical trials.

In this issue, Mingoazzi et al describe the immune consequences of AAV–mediated skeletal muscle gene delivery in humans. Their findings were based on an open-label dose escalation study in which an AAV–1 vector encoding a truncated lipoprotein lipase (LPL<sup>Δ</sup>LPL) was administered into the limb muscles of subjects suffering from LPL deficiency. These patients typically have abnormal lipid breakdown consisting of elevated triglyceride (TG) levels in the blood. A transient decrease in plasma TG levels was apparent in some of the subjects, suggesting a possible therapeutic effect. However, because dietary fluctuations may potentially interfere with TG levels and the number of patients was limited, conclusions regarding efficacy will need to be confirmed in subsequent larger trials.

The authors noted that one of the subjects who received the highest vector dose experienced a transient increase in muscle enzyme creatine phosphokinase (CPK). This elevation in CPK appeared to be associated with a therapeutic effect whereby TG levels transiently returned to baseline. Activation of AAV–1 capsid-specific CD4<sup>+</sup> and CD8<sup>+</sup> T-cell responses may have contributed to the clearance of the AAV–1–transduced muscle fibers. Interestingly, 50% of the subjects enrolled in this trial developed an AAV–1 capsid-specific T-cell response, whereas LPL–specific T-cell responses could not be detected. Increasing vector doses resulted in a more rapid onset of capsid-specific T-cell responses and an apparent shift toward mixed CD8<sup>+</sup> and CD4<sup>+</sup> AAV–1 capsid-specific T-cell responses. In
Allotransplantation in pediatric HL

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