Autologous HSCT for systemic sclerosis

Richard Burt and colleagues (March 30, p 1116)[1] propose from a retrospective analysis of autologous haemopoietic stem-cell transplantation (HSCT) in 90 patients with systemic sclerosis that comprehensive cardiac screening including fluid challenge improves patient selection. They ascribe the higher treatment-related mortality in the ASTIS trial[2] (10% *vs* 6% in their study) to less rigorous cardiac screening, which mandated right heart catheterisation only if there was pulmonary arterial hypertension on echo. However, only three treatment-related deaths in the ASTIS trial[2] (of 79 HSCT patients) were ascribed to heart involvement compared with four treatment-related deaths (of 90 HSCT patients) in the study by Burt and colleagues.[1] The ASTIS trial was a prospective, controlled trial with rigorous independent review of serious adverse events including treatment-related fatalities.[3]

A substantial proportion of patients in the retrospective analysis by Burt and colleagues[1] were treated on compassionate use, and institutional review board approval for these patients was obtained retrospectively. It is questionable whether ascertainment of deaths, serious adverse events, secondary malignancies, and autoimmune diseases (not reported in the study) received a similar level of scrutiny.

Lastly, the authors make the point that HSCT should be considered as first-line treatment for selected patients with systemic sclerosis, but they do not explain which patients, nor corroborate this with evidence. The prognosis of systemic sclerosis has improved due to better care and more effective use of immunosuppressive medication.[4] Given the risks and costs associated with HSCT, more controlled studies are necessary to establish the place of HSCT in systemic sclerosis treatment.

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Richard Burt and colleagues' study[1] of treatment-related mortality of autologous haemopoietic cell transplantation in progressive autoimmune diseases is promising with an acceptable 5% treatment-related mortality, compared with 10% in the ASTIS trial.[2] However, we believe that some issues need to be further clarified.

First, this is a retrospective, non-randomised study done in two centres using two separate groups of patients. Inclusion and exclusion criteria, previous therapies (with alkylating agents or other agents such as bleomycin), substantial comorbidities (such as uncontrolled hypertension), pretransplant performance status, and disease duration have not been included in this manuscript.[1] However, these factors could directly affect the transplant toxicity.

Second, an attempt to further assess cardiac involvement was made in the last 12 patients included in the study, selected in a non-randomised manner. These patients were subjected to enhanced cardiopulmonary screening, including right heart catheterisation, an invasive procedure performed in critically-ill patients. In view of the risk associated with these procedures,[3] their use cannot be accepted as a routine pretransplant work-up.

In conclusion, the role of comprehensive cardiopulmonary screening should be carefully evaluated by a well conducted, multicentre randomised study. More than that, growing experience[4] has shown that optimal timing of transplantation and better selection of patients without progressive disease or severe disabilities are the major steps for improving transplant outcome and lowering unacceptable toxicities.

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Authors' reply

We thank Jacob van Laar and colleagues and Ioanna Sakellari and colleagues for their comments.

Van Laar and colleagues assert that patients treated off study did not receive similar scrutiny as those in either the ASSIST or ASTIS clinical trials. In fact, patients off study were treated and followed before and after transplantation in an identical manner to our patients in the ASSIST trial. Our current results[1] in 90 patients when compared with our previous randomised trial[2] show similar improvement in skin score, forced vital capacity, and quality of life, and now for the first time improvement in diffusion capacity of carbon monoxide in patients with normal pretransplant cardiac function and electrocardiography.

Treatment-related mortality is not a consequence of the autologous stem cells per se but rather the conditioning drugs, patient selection, and centre effects. The 3·8% (3 of 78) cardiac-related mortality in the ASTIS trial described by van Laar and colleagues does not seem significantly different from the 4·4% (4 of 90) cardiac-related mortality reported in our article. This should be cause for concern and motivation to initiate more extensive pretransplant cardiac scrutiny in patient selection. Moving from limited phase 1–2 trials to a large phase 3 trial that included inexperienced centres could result in higher study mortality in the experimental (transplant) group.[3] Could the additional non-cardiac mortality in the ASTIS trial have occurred at less experienced centres?

Concerning the comments by Ioanna Sakellari and colleagues, the two centres used the same protocol, no patient had received bleomycin or alkylating agents (other than cyclophosphamide) because these drugs are not used to treat systemic sclerosis. Table 1 in our paper[1] lists comorbidities such as previous therapies including previous cyclophosphamide treatment, duration of disease, hypertensive renal crises, etc.

Concerning the risks of right heart catheterisation; in Ranu and colleagues' study[4] the rate of complications

was very low (1·7%), and there was no serious complication, consistent with previous studies of right heart catheterisation at experienced centres.[5] Thus, the risk associated with right heart catheterisation to determine accurate pulmonary artery pressures is minimal compared with the risk associated with transplant, especially if a complete pretransplant cardiac evaluation is not done.

We fully agree with more comprehensive cardiac screening, and such screening is ongoing in our ASSIST II randomised trial (NCT01445821).

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