Long-term survivors in severe aplastic anemia: standard mortality rates now comparable to controls?

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In the current issue of *Haematologica*, Nakamura and co-workers report standard mortality rates (SMR) for patients with severe aplastic anemia (SAA) alive one year after receiving either immunosuppressive therapy (IST) or a hematopoietic stem cell transplant (HSCT).[1] SMR compare the mortality risk of SAA patients with the general population, adjusted for age, gender, and race/ethnicity. The bottom line is that 1-year survivors after IST or HSCT can expect to live beyond five or ten years, becoming comparable to that of the general US population. Severe aplastic anemia is a rare hematologic disorder, which was, in the 1970s, lethal in most cases.[2] The outcome has improved considerably over the past decades with the widespread use of IST and HSCT. What remains to be ascertained is the long-term outcome of these therapeutic procedures, particularly since both have long-term complications: 20% cumulative incidence of tumors has been reported 12 years after IST and 5% after HSCT.[3] Chronic graft-*versus*-host disease (cGvHD) after HSCT and persistent transfusion requirement/relapse after IST are also well-known complications, together with non-lethal issues such as osteonecrosis, fertility problems, cataracts, hypothyroidism. For these reasons, the long-term outcome of SAA patients has been regarded as never reaching the contemporaneous control curves.

There are several findings which I find surprising in the study of Nakamura and co-workers:[1] first, the fact that SMR normalized after a given time post treatment; second, that this is true both for IST as well as for HSCT; and third, that alternative donor transplants seem to have similar SMR to matched sibling transplants. As to the gradual reduction of the SMR in 5- and 10-year survivors, this tells us that patients are still at a higher risk of lethal complications between one and five years, including failed response for IST and cGvHD for HSCT; however, it also suggests that patients who survive five years, especially over the last decade, can be considered to be cured of their disease. So, a combination of bad and good news.

Treatment with IST has never been regarded as curative, and the term "postponing the inevitable" was defined many years ago,[4] being the inevitable clonal evolution into myelodysplasia or overt leukemia. This study now suggests that patients surviving five years following IST can expect a similar survival to the control population, although a proportion (20%) of IST patients did receive an allograft for incomplete response.

Finally, we learn that alternative donor transplants have similar long-term outcome, in terms of SMR at 5-10 years, to that of matched sibling grafts. This is an important confirmation of comparable survival,[5] but also confirms that for patients who lack an HLA matched sibling, an unrelated transplant should be considered early in the course of the disease. A very recent analysis of the SAA Working Party of the European Group for Blood and Marrow Transplantation (EBMT) has shown rather convincingly that patients allografted upfront from an HLA matched related donor have a significantly better outcome than patients allografted after having failed IST;[6] this is true for patients under the age of 40, and also for subgroups of patients over the age of 40 years.

The Authors admit that more patients need to be studied, and with longer follow-up, especially for more recent patients, and that causes of death in the first five years after treatment need to be carefully evaluated. Nevertheless, a gradual reduction of SMR to approximately that of the general population is, for a rare, once lethal disease, a great achievement of the scientific community.

Disclosures

No conflicts of interest to disclose.

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