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Bone marrow transplantion for severe aplastic anemia from HLA identical siblings

Early bone marrow transplant (BMT) studies, in the fifties and sixties, produced important results, some of which are listed here:

a. marrow given intravenously is as effective as marrow given by any other route;[1]
b. marrow is an immunologically competent organ and can mount a reaction against the host;[1]
c. cyclophosphamide alone can provide sufficient immunosuppression for engraftment of allogeneic stem cells.[2]

Clinical programs of allogeneic BMT for severe aplastic anemia (SAA) have developed along these major lines.

Cyclophosphamide 200 mg/kg and graft rejection

The conditioning regimen developed at the John Hopkins hospital by George Santos, which used 200 mg/kg cyclophosphamide, appeared to be attractive for BMT in patients with SAA. Initial results were encouraging but graft rejection was a major problem: in the first large series published the risk of rejection was 21/73 patients (29%).[3] This produced survival rates not exceeding 40-50%.[3]

There are at least 5 factors associated with graft rejection:

1. the intensity of the conditioning regimen. The addition of total body irradiation (TBI) or thoracoabdominal irradiation (TAI) reduces the risk of rejection to 3%.[4-6] The dose of irradiation is also important: 6 Gy[5] being more effective than 3 Gy;[6]
2. the number of stem cells infused. Patients receiving more than 3.5×10^8/kg marrow cells have a lower risk of rejection.[3] In 1978 Rainer Storb wrote: "*it seems important to obtain the largest possible number of marrow cells from the anterior and posterior iliac crests; because there is a limit to the quantity of cells we can harvest from a donor, we need to explore alternative sources such as the peripheral blood*";[7]
3. the number of infused T-cells. Adding peripheral blood leukocytes from the donor (so called buffy coat) on day +1, +2 significantly reduces the risk of rejection, possibly because of the combined effect of additional lymphocytes and stem cells. If the marrow is T-cell depleted, then the dose of cyclophosphamide 200 mg/kg is insufficient and one needs to deliver 18 Gy total lymphoid irradiation to achieve engraftment.[8];
4. post-BMT immunosuppression. When methotrexate (MTX) is given post-BMT, the rejection rate is between 15% and 30%. The introduction of cyclosporin A (CyA) has reduced rejection to less than 10%,[9] and the combination of the two (CyA+MTX) further reduces the risk to the current 7%;
5. donor/recipient HLA matching. In the setting of HLA identical sibling transplants, in which donor and recipient are genotypically identical for the major histocompatibility complex region on chromosome 6, rejection is 7-15%. But for alternative donor grafts, either family mismatched or unrelated, the risk of rejection exceeds 20%. This has been extensively proven in an experimental animal model.

In brief, rejection can be prevented by high numbers of stem cells, intensive conditioning regimens including radiation, and high numbers of donor lymphocytes.

Graft rejection and donor chimerism

Sensitive molecular biology techniques to detect donor/recipient chimerism have shown that the gap between engraftment and rejection is filled by mixed

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chimerism, which can be transient, persistent, or progressive: over 20% of long term survivors are mixed chimeras and close monitoring of chimerism can reveal important information on the requirement for immunosuppressive therapy.[10]

Graft-versus-host disease

Some (but not all) measures which reduce rejection will increase the proportion of patients with full donor chimerism, and therefore increase the risk of graft-versus-host disease (GvHD). Patients receiving radiation have a greater risk of acute GvHD, and chronic GvHD, including pneumonitis.[11] Patients receiving donor buffy coat cells post-BMT have a greater risk of GvHD.[12] In the case of increased risk of GvHD the overall outcome is not improved.

On the other hand some measures may reduce both rejection and GvHD:

1. additional immunosuppression pre-BMT (anti-thymocyte globulin);
2. selection of a genotypically identical sibling;
3. high numbers of stem cells.

In order to improve the outcome one would want to favor these rather than the former.

Radiation and second tumors

The Seattle group has shown that dogs exposed to radiation have a greater risk of tumors after transplantation,[13] and therefore has avoided the use of TBI in patients with SAA. The group in Saint Louis introduced thoraco-abdominal irradiation in the early eighties, with a single fraction of 6 Gy:[5] this regimen provided two advantages, the reduction of the dose of cyclophosphamide from 200 mg/kg to 150 mg/kg (thus eliminating cardiac toxicity) and the significant reduction of rejection. Although initial survival was encouraging, there was an increased risk of pneumonitis,[11] of chronic GvHD and of second tumors.[14] The Paris group has now abandoned the use of radiation both in patients with acquired or constitutional aplasia, owing to a 20% risk of tumors by 20 years after BMT.[14] The lesson from the radiation studies in 1998 is therefore clear: radiation should not be used in patients with SAA in the setting of HLA identical sibling transplants, because it does not improve the outcome but exposes the patient to an increased risk of late effects including infertility and second tumors.

Current results

Currently, greater than 70% survival can be achieved in HLA identical sibling transplants.[15,16] In the present issue, Hernández-Boluda *et al.*[17] confirm these data and conclude that BMT is particularly effective in young patients with SAA.

The current transplant protocol should include: a) cyclophosphamide 200 mg/kg as part of the conditioning regimen; b) cyclosporin A and methotrexate as GvHD prophylaxis; c) bone marrow as the stem cell source. The addition of anti-thymocyte globulin (ATG) in the conditioning regimen has been reported to further increase the survival to over 90%, by reducing the risk of rejection and GvHD.[16] The use of peripheral blood allogeneic stem cells is probably unnecessary due to the excellent current results, and to the increased risk of chronic GvHD.[18]

Future goals

For the future I see two major areas of intervention: increasing the upper age limit of patients (currently between 40 and 50) and expanding the donor pool to unrelated subjects. Both will need better control of transplant complications and better understanding of genetically determined immune reactions.

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