Aplastic Anemia: Pathogenesis and Treatment

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Key Words

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Summary

Treatment of severe aplastic anemia (SAA) in Europe between 1970 and 1986 is reviewed. 487 patients received an HLA-identical BMT: results are encouraging and currently suggest a 65% survival. However, many patients cannot be offered this procedure because of the absence of an appropriate donor. Forty-five patients were given a non-HLA identical BMT: results are dependent on the degree of mismatch. Immunosuppression (IS) was given to 509 patients: 50% of these survive. Some mechanisms regulating in vitro hematopoiesis are discussed, together with their relevance in the treatment of SAA.

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Zusammenfassung und Schlüsselwörter

Die Behandlung der schweren aplastischen Anämie in Europa, in den Jahren 1970 bis 1986, wird diskutiert. Bei 487 Patienten wurde eine Knochenmark-Transplantation (BMT) von einem HLA-identischen Geschwister durchgeführt. Die Ergebnisse sind ermutigend, da zur Zeit 65% überleben. Es besteht allerdings das Problem, daß viele Patienten keine Geschwister haben; für diese Fälle muß man eine Alternative finden. Nicht-HLA-identische BMT wurden bei 45 Patienten durchgeführt. Das Überleben hängt vom Grad der HLA-Unverträglichkeit ab. Eine immunsuppressive Behandlung (IS) wurde in 509 Fällen versucht: 50% überleben noch. Die Mechanismen, die die in-vitro-Hämatopoese regulieren, werden zusammen mit ihrer Beziehung zur Behandlung der SAA diskutiert.

Aplastische Anämie – Knochenmarktransplantation – Hämatopoese

Severe aplastic anemia (SAA) is a complex hematological disorder, characterized by severe pancytopenia and an empty marrow. In the majority of patients there is no evident cause for the disease, in 20% of patients there is a preceeding viral infection – often hepatitis – and in a third group there is a history of exposure to either a potentially hazardous toxic agent (benzene) or a drug (such as cloramphenicol). If untreated, the disease is fatal in over 70% of the cases. We shall briefly review here the present standing of treatment in Europe, as analyzed in 1986 from data in the European Bone Marrow Transplantation (EBMT) Registry, and then describe some aspects of the biology of the disease, derived from in vitro studies on hemopoietic progenitors. HLA-identical Bone Marrow Transplantation

The SAA EBMT Registry now contains 487 patients given an HLA-identical BMT. The survival rate has been improving over the past years from 40% in 1970–75 to 63% in 1981–85. The use of cyclosporin A (CS) appears to offer an advantage over methotrexate (MTX) (67% vs. 53%), not because of a reduced incidence of acute graft versus host disease (GvHD), but rather because of a lower incidence of infections, possibly due to faster engraftment.

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Graft rejection is no longer the major problem of BMT for SAA: it used to represent 50% of all deaths in the early **1970s**. It is now down to 10% of all deaths, and in absolute numbers it only occurs in less than 5 % of patients. The improvement is due partly to the use of CS, and partly to pre-graft nodal irradiation: the conditioning regimen with the highest survival rate includes cyclophosphamide 150 **mg/kg** B.W. and thoraco-abdominal irradiation (a protocol originally designed by Eliane Gluckman in Paris). Optimal selection of patients and early transplants will further improve these results in the coming years.

Non-HLA-**I**dentical **I** BMT

Forty-five patients received a graft from a donor other than an HLA genotypically-identical sibling. The overall survival rate is 23 %. However, significant differences can be observed depending on the conditioning regimen (the use of irradiation (30% survival rate) is superior to regimens without irradiation (15% survival rate)), and especially on the degree of HLA identity between donor and recipient: phenotypically-identical grafts show a 39% survival rate, which is certainly superior to the 14% of 1–3 loci mismatches, and also not terribly far from results obtained in the genotypically-**matched** situation. A phenotypically-**matched** graft, also from an unrelated donor (no difference between family or unrelated donors, given comparable degrees of compatibility), can be considered in some cases of SAA in which other therapies either have not worked or are unlikely to produce a response.

Bacigalupo et al.: Aplastic Anemia: Pathogenesis and Treatment

173

Immunregulation der Hämatopoese

Immunosuppressive Therapy

Five hundred and nine patients are registered as having been treated with **immunosuppression** (IS), in the large majority of cases including antilymphocyte globulin (ALG). The overall survival rate, with follow-up exceeding 120 months, is currently 50%. The plateau is reached beyond the fifth year, indicating that some patients still die as a consequence of the disease long after treatment, and that many are not completely cured and are at risk of relapse.

Clinical signs of hemorrhage and infections at the time of treatment are important in determining the final outcome: patients with and without hemorrhages and infections have a 77% vs. 33% survival rate, respectively. The same can be said for the degree of granulocytopenia: patients with less than 200 neutrophils/mm³ have a survival rate of 38% compared to 64% for patients with neutrophil counts between 200 and 500/mm³. A multivariate analysis is in progress to determine which patients are at high risk of early death: this will hopefully help identify patients who then will be eligible for different forms of treatment, such as partially mismatched BMT.

Biology of Aplastic Anemia

One interesting observation derived from IS treatment is that over 50% of SAA patients fulfill two criteria: enough residual stem cells and appropriate conditions for hemopoietic reconstruction. With optimization of supportive care a large majority of SAA patients given ALG is

likely to survive. Unfortunately, since it is uncertain by which mechanism ALG promotes hemopoietic reconstitution, it is also unclear why some patients fail to recover.

Although one cannot readily identify responders before treatment with ALG, at 1 month post-treatment patients who will respond show a greater enhancement of colony growth after T-cell depletion. The test can be performed by mechanically removing T cells by E rosetting: it is not easy to reproduce by means of monoclonal antibodies and complement. This suggests that concentration of progenitors by removal of a large number of T cells may be partly responsible for the effect observed. This, together with the difficulty of processing adequate numbers of bone marrow cells from aplastic patients, indicates that other tests are needed to identify responders early, possibly before treatment.

We have been looking at various agents, and at their effect on colony formation in SAA patients, as well as in normal individuals. We have been unable to enhance colony growth in SAA patients by administering anti-T-cell monoclonal antibodies, acyclovir, cyclosporin A, interferon, interleukin 2, ALG, and recently haploidentical normal T cells. The latter experiments were set up to test whether a “helper” activity, defective in

SAA patients, could be transferred with haploidentical T cells. A relevant increase in colony formation could be observed, but dose/response experiments with decreasing numbers of normal T cells indicated that aplastic anemia marrow cells were boosting colony formation of “contaminating” myeloid cells in the T-cell suspension, and not vice versa. We are at present continuing to look at different agents, also in different culture conditions, such as long-term cultures. Suppression of colony growth occurs in a number of patients and can be demonstrated on autologous as well as on allo-genetic normal progenitors. Patients who exhibit suppression, via a T-cell-derived lymphokine which we refer to as T-cell-derived colony inhibiting activity (Td/CIA), are the ones who proceed to a good response to ALG. Testing for allogeneic suppression is easier than enhancing autologous growth, requires fewer cells, and can be done in almost every patient before and after treatment. Again, the effect is more evident 1 month post-ALG, thus raising the question of its significance. We have chosen to study BMT chimeras as a model for early hemopoietic reconstitution, mostly to assess whether or not suppression could be identified also in these patients. We could not detect suppressor T cells, neither by autologous nor by allogeneic co-cultures. Thus chimeras behave differently from SAA patients, and probably cannot be taken as a model for hemopoietic reconstitution of aplasia. This also points out the differences between the two conditions: in chimeras the immune system is severely impaired in its function, whereas in SAA the immune system is quite intact, and as we have shown in previous studies, possibly ‘activated’.

Whether suppressor T cells play a role in the pathogenesis of aplastic anemia or in the hemopoietic reconstitution is unclear. What has emerged vigorously from the investigations on soluble and cellular inhibitors/promoters, is that the final result of stem-cell proliferation/differentiation will depend on the balance among these < environmental > conditions. We must continue to study cell populations at the purest possible level (clones) to ascertain their actual role in the regulation of stem-cell growth. Hopefully we shall be able to identify techniques by which colony formation can be enhanced. At that point it will be easy to differentiate patients and select better forms of treatment for each group.

Acknowledgment

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