target cells may coexist. Under these circumstances, future investigations will help clarify the division of labor among NK-cell subsets. Although further studies are necessary to more fully understand NK-cell responses to target cell recognition, the work by Fauriat et al sheds light on the functional heterogeneity of human CD56bright and CD56dim NK-cell subsets. This study also advances our knowledge on how multiple NK cell–activating receptors contribute to cytokine and chemokine production of CD56dim NK cells upon target cell recognition. The authors show that CD56dim NK cells produce IFN-γ, rather than CD56bright NK cells, upon target cell recognition. Interestingly, less than 10% of CD56dim NK cells are IFN-γ–producing cells upon target cell recognition, while the majority of CD56bright NK cells produce IFN-γ upon cytokine IL-12 and IL-18 costimulation. A recent study by Yu et al identifies a functional intermediary between CD56bright and CD56dim NK-cell subsets, which is CD56dim phenotype and produces IFN-γ when stimulated by target cell (K562) recognition or cytokine costimulation with IL-12 and IL-18. This finding provides evidence that CD56bright NK cells might be the precursors of CD56dim IFN-γ–producing cells, which become fully functional in terms of cytokine production and cytotoxicity upon recognition and lysis of cellular targets, including tumor cells. However, further studies are necessary to investigate whether these observations are both developmentally and functionally related. These studies will help us to fully understand the mechanisms of immune differences between CD56bright and CD56dim NK-cell subsets.

Acknowledgment: We thank Dr Brian Becknell for critical reading and editing of the manuscript.

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

REFERENCES

Comment on Brodsky et al, page 2136

Cyclophosphamide in aplastic anemia?

Gerard Socié HÔPITAL SAINT LOUIS

The use of high-dose cyclophosphamide without stem cell support has been proposed by physicians at John Hopkins University Hospital for many years as treatment for patients with newly diagnosed or refractory aplastic anemia. In this issue of Blood, Brodsky and colleagues report the long-term follow-up of their single-center clinical trial.

Aplastic anemia is a rare but heterogeneous disorder. The majority (70%-80%) of these cases are categorized as idiopathic because their primary etiology is unknown. Allogeneic bone marrow transplantation (BMT) from an HLA-identical sibling donor is the initial treatment of choice for newly diagnosed young patients if they have severe or very severe aplastic anemia, and have an HLA-compatible sibling donor. Data from retrospective studies and from prospective randomized clinical trials conducted 20 years ago lead to the following recommendations1-2:

1. (Transplantation should be performed as soon as possible before infections and transfusion immunization occur.
2. The recommended source of stem cells is bone marrow (and not peripheral blood).
3. There is no indication for using irradiation-based conditioning regimens for patients undergoing HLA-identical sibling BMT and the reference conditioning is high-dose cyclophosphamide (200 mg/kg) plus antithymocyte globulins (ATG).
4. (Graft-versus-host disease prophylaxis should be cyclosporine plus methotrexate (superior to cyclosporine alone).

If physicians follow these worldwide-accepted recommendations, then transplantation for severe aplastic anemia from an HLA-identical sibling donor can be very successful with an 80% to 90% chance of long-term cure.

If the patient does not have an HLA-identical sibling donor, then the treatment of choice is immunosuppressive therapy. Data coming mostly from randomized clinical trials allow firm recommendations3-4:

1. (The combinations of ATG and cyclosporine is the reference treatment for patients with both severe and nonsevere disease.
2. Prednisone must be given for only a short period of time to prevent the serum sickness syndrome.
3. Granulocyte colony-stimulating factor does not improve response rates when added to ATG plus cyclosporine and does not decrease infection rates in randomized trials.

The outcome after standard treatment with ATG plus CSA (60%-70% response rate and 70%-80% long-term survival probability) is currently excellent. However, after such treatment, only roughly one-third of the patients are cured (of treatment with normal blood counts), one-third are dependent on long-term administration of cyclosporine, and one-third will either relapse or develop a clonal disorder (myelodysplastic syndrome [MDS] or acute myeloid leukemia [AML]). Thus, any aim to compare results between different treatments in aplastic anemia should use event-free survival (EFS) estimates (where death, relapse, MDS/AML, BMT, or paroxysmal nocturnal hemoglobinuria requiring treatment are defined as events) that give a better picture of treatment efficacy.

Unfortunately, recent clinical trials from Dr Young’s group at the National Institutes of Health (NIH) strongly suggest that adding either mycophenolate mofetil3 or sirolimus4 to ATG plus cyclosporine does not increase the benefit of the standard treatment. Thus, there is an urgent need for treatment modalities that improve EFS after immunosuppressive therapy with ATG plus cyclosporine that has been described more than a decade ago!
In this issue of Blood, Brodsky and colleagues report the long-term follow-up of their single-center clinical trial using high-dose cyclophosphamide alone (without stem cell support) in patients with either treatment-naive (n = 44) or refractory (n = 23) disease. At 10 years, the overall actuarial survival rate was 88%, the response rate was 71% and the actuarial event-free survival rate was 58% in 44 treatment-naive patients. Patients with refractory severe aplastic anemia fared less well: at 10 years, overall actuarial survival, response, and actuarial event-free survival rates were 62%, 48%, and 27%, respectively.

Thus, taking into account only naive patients, results from the Hopkins group are in the high-level range of reported results, at first glance. However, actuarial failure-free survival rate confidence intervals (40%-74%) at 10 years are only slightly better or within the range of treatment results with ATG plus cyclosporine. However, using high-dose cyclophosphamide led to long-lasting cytopenias (median time to response, 5 months [2 to 10 months]). As a consequence, the cumulative incidence of fungal infections was of some concern. Severe fungal infections occurred at a rate of 18.2% in the 44 treatment-naive patients. The cumulative incidence of developing such an infection was 21%. In contrast, 10 (43.5%) of the 23 refractory patients acquired a severe fungal infection, corresponding to a 2-month cumulative incidence for fungal infection of 39%.

The authors conclude that “large randomized controlled trials will be necessary to establish how results of high-dose cyclophosphamide compare with either bone marrow transplantation or standard immunosuppressive regimens with ATG and cyclosporine.” That is clearly the issue of this study. An NIH prospective, randomized study comparing its use in combination with cyclosporine against the “gold standard” of ATG and cyclosporine was terminated prematurely because of an excess of early deaths and systemic fungal infections in the cyclophosphamide arm. The use of cyclophosphamide was associated with profound and very prolonged pancytopenia resulting in a significant increase in the use of blood and platelet transfusions, days of intravenous antibiotics and antifungal drugs, and inpatient days in hospital.

Whether a trial (high-dose cyclophosphamide vs ATG + cyclosporine) will ever be done in a multi-institutional setting is thus highly unlikely! Also, the randomization of a patient with a sibling donor between high-dose cyclophosphamide and transplantation raises, in my opinion, ethical concern.

In summary, should high-dose cyclophosphamide be used in aplastic anemia? Maybe, maybe not. We are still facing significant uncertainties!

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

Comment on Murga Penas, page 2214

V(D)J recombination and staggered DNA breaks: guilty again

Francisco Vega and L. Jeffrey Medeiros M. D. ANDERSON CANCER CENTER

In this issue of Blood, Murga Penas and colleagues describe mechanisms involved in the genesis of the t(14;18)(q32;q21)/IgH-MALT1 in MALT lymphoma, and they identify a cluster region suitable for detection by polymerase chain reaction.

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue, also known as MALT lymphomas, arises in extranodal sites. The most common sites are stomach, lung, skin, ocular adnexae, salivary glands, and thyroid gland, but virtually any extranodal site can be involved. MALT lymphoma is a prototype for antigen-driven B-cell lymphomagenesis. Antigens involved in lymphomagenesis result from either chronic infection (eg, Helicobacter pylori in stomach) or autoimmune diseases (eg, Hashimoto thyroiditis, Sjogren syndrome). Most extranodal sites involved by MALT lymphoma normally lack lymphoid tissue. Chronic antigenic stimulation results in these sites acquiring lymphoid tissue, within which MALT lymphomas can arise.

Chromosomal translocations, usually resulting in oncogene activation, occur in many types of lymphoma, and their detection is helpful for establishing a diagnosis and monitoring disease after therapy. In MALT lymphomas, a total of 10 chromosomal translocations have been reported, of which 4 are well characterized and implicated in pathogenesis, with 6 more recently described and variably defined. These translocations are mutually exclusive in an individual MALT lymphoma and correlate with site of disease.

MALT lymphomas associated with t(11;18) arise most often in the stomach and lung. In contrast, MALT lymphomas associated with t(14;18) arise commonly in the thyroid gland, skin, and the ocular adnexae; and MALT lymphomas associated with t(3;14) tend to occur in the thyroid gland, skin, and the ocular adnexae; and MALT lymphomas associated with t(1;14) may have a predilection for the intestines. The heterogeneity of MALT lymphomas, in their site of origin, associated diseases, and translocations, suggests that MALT lymphoma is actually a number of different, but related, diseases.
Cyclophosphamide in aplastic anemia?

Gerard Socié