Aplastic Anemia

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Introduction

Aplastic Anemia (AA) is defined as pancytopenia with a hypoplastic bone marrow. The incidence of acquired AA in North America is approximately 2/million/year. The incidence appears to be 2-3 times higher in Asia [1, 2].

Etiology

The majority of cases of AA are idiopathic in nature. There is however an association with other autoimmune disorders such as rheumatoid arthritis and in particular the rare disorder eosinophilic fasciitis. In 1/4 - 1/3 of patients a drug or toxin can be implicated. There are numerous drugs that have been associated with individual case reports of AA, however some of the more classically implicated drugs include chloramphenicol, sulfonamides, chloroquine, gold salts, indomethacin, and thiouracil. There is also an increased incidence of viral infections, in the few months preceding the diagnosis of AA, most notably viral hepatitis (non A, non B, non C) [1, 2].

Pathophysiology

Regardless of the instigating event, the physiology driving the pathology of aplastic anemia appears to be autoimmune in nature. Natural killer T cells (CD4-/CD8-), which are believed to play a role in immune regulation, are found to be suppressed in patients with AA. Furthermore patients with AA have been shown to express an increase in cytotoxic effector T cells (CD8+/CD3+) with subsequent elevations in TNFα and IFγ which can in turn induce Fas-mediated apoptosis of hematopoietic stem cells. Interestingly, this immune profile has also been demonstrated in patients with hypoplastic MDS [3, 4].

Diagnosis

It is typically very difficult to make the diagnosis of aplastic anemia on symptoms and initial blood work alone, as there are many causes of pancytopenia that could present with a similar clinical scenario. Congenital aplastic anemia (Fanconi's anemia) is occasionally not diagnosed until early adulthood, and should be excluded especially in younger patients. Primary hematologic malignancies or secondary infiltration of the bone marrow by metastatic tumour or infections should also be ruled out on bone marrow examination. Acquired primary bone marrow failure syndromes such as myelodysplasia (MDS), myelofibrosis and paroxysmal nocturnal hemoglobinuria (PNH) can also be very difficult to distinguish from AA, especially the hypoplastic variant of myelodysplasia. Approximately 10% of patients with AA can have abnormal cytogenetics at the time of their initial bone marrow examination, however evidence of dysplasia in megakaryocyte and granulocyte lineages, or the presence of monosomy 7 should alert the physician to the possibility of hypoplastic MDS. Of note, up to one quarter of patients with AA may have evidence of a clonal population on flow cytometry consistent with PNH. If this clone is of low level, and there is no evidence of hemolysis or thrombosis, these patients should be treated similarly to patients with pure aplastic anemia [1].

Baseline Investigations

All patients should have the following investigations at the time of diagnosis:

- CBC, differential, reticulocyte count
- Blood film
- Renal profile, liver profile, LDH
- Ultrasound abdomen
- Bone marrow aspirate and biopsy with cytogenetics
- Flow cytometry for PNH (NB: notify flow lab as sample needs to be processed within 4 hours)
- Vitamin B_{12} and RBC folate
- Peripheral blood cytogenetics for Fanconi's anemia if < 35 years old
- Hepatitis B and C serology
- HIV Serology
- Serology for autoimmune disorders should only be drawn if there is a clinical indication other than aplastic anemia

Patients who are less than 55 years of age, and are eligible for bone marrow transplant should have HLA typing performed, as well as HLA typing of any potential sibling donors at the time of diagnosis. They should also be screened with additional viral serology for CMV, EBV and HSV.

Classification

Non Severe Aplastic Anemia	Severe Aplastic Anemia	Very Severe Aplastic Anemia
Patients do not fulfill the criteria for very severe or severe AA, but do present with prolonged pancytopenia, hypoplastic bone marrow examination with no other attributable cause	Patient must meet the following criteria: (a) Bone marrow cellularity < 25% Or 30-50% with < 30% residual hematopoietic cells (b) Two of three of the following: (1) Neutrophils < 0.5×10^9/L (2) Platelets < 20×10^9/L (3) Reticulocytes < 20×10^9/L	Patient must meet the criteria for severe aplastic anemia and have: Neutrophils < 0.2×10^9/L

Treatment Options

1. Antithymocyte or Antilymphocyte Globulin with Cyclosporin

Both ALG/ATG and cyclosporin have been shown to be active agents in AA with overall response (ORR) to either agent alone of 40%–50% [5-7]. However the combination of ALG/ATG with cyclosporin in phase II studies has been shown to have superior outcomes with ORR rates of 58%–80% [8-11]. Furthermore, in phase III randomized control trials, the combination therapy of ALG with cyclosporin has been shown to be superior to ALG alone (ORR 41% vs 70%) and to cyclosporin alone (ORR 46% vs 74%) [6, 12]. Therefore, the combination of ATG/ALG with cyclosporin has become the standard first-line immunosuppressive therapy for patients with Aplastic Anemia [1, 13, 14].

2. High Dose Cyclophosphamide

Cyclophosphamide has been shown to have activity as a single agent in patients with AA with ORR of 46%-73% [15]. However in a randomized control trial comparing the combinations of high dose cyclophosphamide with cyclosporin to ATG with cyclosporin the cyclophosphamide arm proved inferior mainly based on prolonged cytopenias as well as excess early deaths and systemic infections [16, 17]. Based on current evidence, routine use of high-dose cyclophosphamide without stem cell support is not recommended, however there is a paucity of data on this treatment option in patients who have failed more than one cycle of immunosuppressive therapy. Therefore we recommend high dose cyclophosphamide (45 mg/kg/day x 4 consecutive days) should only be considered for patients who have failed first and second-line immunosuppressive therapy who are ineligible for allogeneic bone marrow transplant, and for which there are no investigational protocols available. In these circumstances, high dose cyclophosphamide should be given with stem cell growth factor support.

3. HLA Identical Sibling Allogenic Bone Marrow Transplant

Allogeneic bone marrow transplantation (AlloBMT) is effective in achieving durable remissions in most patients with AA to which it is applied. Given the high rate of long-term relapse and secondary hematologic malignancies associated with immunosuppressive therapy alone, it is also considered the only curative treatment option. There is however a high rate of toxicity associated with AlloBMT with higher rates of graft failure and chronic graft versus host disease than seen in patients undergoing AlloBMT for other hematologic malignancies. Early single centre series published from the 1970's documented long term survival rates of 40% to 50%. Over the last three decades these survival rates have improved dramatically to 75%-90%. Most series have shown a survival advantage of AlloBMT over immunotherapy alone, however these results are undoubtedly biased by patient age and selection and AlloBMT has never been compared to immunotherapy alone in a randomized fashion. Furthermore, as success rates for both treatment options have improved in the last few decades, several single centre series have not shown a statistically significant difference in overall survival between AlloBMT and immunotherapy alone [1, 18-22]. Our policy is to recommend a related AlloBMT as first-line therapy in all young patients (< 40 years old) with an HLA identical sibling and who are otherwise medically eligible for bone marrow transplant. In older patients related AlloBMT should be reserved for those who have failed first-line immunotherapy or who have developed a significant secondary hematologic malignancy.

4. Unrelated Matched Allogenic Bone Marrow Transplant

Unrelated bone marrow transplantation is still considered controversial in patients with AA, as it is associated with a high rate of morbidity and mortality. It may be considered on an individual basis in patients less than 55 years old, who are otherwise healthy and who have failed one or more lines of ATG-containing immunosuppressive therapy [1, 22].

Prognosis

Over the last few decades, we have improved outcomes in patients with AA dramatically. Currently patients have an estimated 5-year overall survival of 75-90% regardless of first-line treatment options. Patients treated with AlloBMT are considered cured of the AA, however there can be many late complications with graft versus host disease and graft rejection. Immunosuppression alone is associated with a high relapse rate, however most patients can be salvaged with repeat courses of immunosuppression or AlloBMT as second-line therapy. The majority of morbidity and mortality in patients with AA occurs due to infectious complications, predominantly in patients who experience prolonged episodes of neutropenia [1, 11, 13, 14].

Follow-up Post Immunosuppression

It may take up to three months to see a clinical response to one course of ALG/ATG; therefore change in therapy should be delayed until this interval has elapsed. If there has not been an adequate response (i.e. transfusion independence) by three months post treatment, a second course of ALG/ATG can be administered with up to a 60% response rate [23].

Relapse rates after treatment with immunosuppressants alone are common and can occur in up to 30%-40% of people, however most patients can respond to increasing doses of cyclosporin or repeat administration of ALG/ATG. A minority of patients may be dependent on cyclosporin long term in order to maintain adequate blood counts. The long term overall survival using immunosuppression alone at 10 years is approximately 50%-60% [1, 8, 9, 11, 12].

Additionally 10-15% of patients with AA may develop a new diagnosis during long term follow-up after immunosuppressive therapy such as new chromosomal abnormalities, PNH, MDS or acute leukemia. In patients with AA the development of new chromosomal abnormalities without a change in clinical status may not always be relevant, and may actually be transient, however patients who develop clinically significant MDS, leukemia or chromosome 7 deletions have a very poor prognosis [1, 8-12, 24].

Follow-up should consist mainly of clinical examination and peripheral blood counts with careful attention to potential long-term treatment related organ toxicities especially in patients on chronic therapy with cyclosporin. Screening for PNH with peripheral blood flow cytometry should be done annually and at time of suspected relapse. Repeat bone marrow examination with cytogenetics to investigate for MDS/AML should be reserved for patients who exhibit clinical relapse in their peripheral blood counts.

Odette Cancer Centre Policy (See flowchart on page 7)

Summary: First-line patients who are less than 40 years of age, and have an HLA identical sibling should be offered AlloBMT as first line therapy if they are otherwise a transplant candidate. Patients over the age of 40, or who don't have a sibling match should be offered immunosuppression with ATG [Horse ATG (Atgam®) at 40 mg/kg daily x 4 days] and cyclosporin [5 mg/kg/day] as first-line therapy. Second-line patients who don't respond to the first course of ATG may respond to a second course, however thereafter alternative therapy should be considered. When using a second course of ATG it is prudent to change to the rabbit derived ATG [Thymoglobulin® 3.75 mg/kg daily x 5 days] due to the potential of previous sensitization to the horse product. If patients are less than 70 years of age and have an HLA identical sibling they should be offered AlloBMT. Patients less than 70 years of age without an HLA identical sibling should be considered for unrelated AlloBMT on an individual basis. If patients are not transplant eligible, investigational agents should be considered.

Supportive Care

Erythropoietin

The majority of patients with severe or very severe AA have high endogenous erythropoietin levels and thus do not respond significantly to exogenous erythropoietin. Therefore the routine use of erythropoietin alone or in combination is not recommended [1, 25, 26].

Granulocyte Colony Stimulating Factor (G-CSF)

The majority of mortality in patients with aplastic anemia can be attributed to infectious complication. In contrast to the use of erythropoietin, patients with AA do respond to G-CSF even when they are severely neutropenic. There have been several randomized controlled trials that have shown improved and faster neutrophil recovery in patients receiving G-CSF, however they have not shown a statistically different rate of overall response, infectious episodes or overall survival [1, 13, 25-28]. Therefore we recommend the use of G-CSF should be limited to short courses to aid in the treatment of severe systemic infections.

Transfusions

Historically patients with aplastic anemia have had a high rate of alloimmunization, especially to platelet antigens, due to repeated transfusion of blood products. Since universal leukodepletion of blood products has been in practice the rate of alloimmunization had decreased to 10-15%, however, in many patients it can still pose a significant clinical problem. We recommend transfusions for symptomatic anemia only, and for platelet counts less than $< 10 \times 10^9$/L or for symptomatic bleeding. Antifibrinolytic therapy is often useful for mucosal bleeding with platelet counts $> 10 \times 10^9$/L. Patients who are potentially eligible for allogeneic bone marrow transplantation should receive blood products negative for Cytomegalovirus (CMV) if their CMV serology is consistent with no prior exposure. Irradiated blood products are not necessary as there have been no cases of transfusion related graft versus host disease in patients with aplastic anemia since the institution of leukodepleted blood products [1].

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ODETTE CANCER CENTRE POLICY FOR THE TREATMENT OF APLASTIC ANEMIA

Severe or Very Severe Aplastic Anemia