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Management of Acquired Aplastic Anemia in Children

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Abstract

The diagnosis of aplastic anemia in children remains exclusion of a variety of inherited or acquired bone marrow failure diseases with similar phenotypes. Urging an efficient diagnostic plan is important because time from diagnosis to “final” treatment is directly related to outcome regardless of the therapeutic option chosen**.** The golden standard of therapy remains hematopoietic stem cell transplantation with marrow derived graft for those children with matched sibling donor. The high response and markedly improved overall survival rates of combined immunosuppressive therapy have proven robust especially with horse derived Anti Thymocyte Globuline + Ciclosporine-A for those without a sibling donor. Incomplete response, relapse, and progression to myelodysplasia/leukemia however have emerged as significant long-term issues. Improvements in outcome of alternative donor transplantation and the use of established and novel immunosuppressive agents provide multiple alternatives for treating refractory or relapsed patients. Regardless of the type of therapeutic approach, patients require centralized treatment in a centre of excellence, ongoing monitoring for recurrence of disease and/or therapy-related immediate side effects and long term effects.

Introduction

Aplastic Anemia (AA) in childhood is an uncommon but serious disorder, which affects approximately two in 1,000,000 children each year. The majority of these cases are categorized as idiopathic because their primary etiology is unknown. In approximately 15-20% of patients the disease is constitutional / inherited where it can present with one or more other somatic abnormalities.

Diagnosis

All children presenting with pancytopenia should be carefully assessed to establish the cause of the cytopenia in childhood which may be different from causes in adulthood. Theses causes might include hypocellular acute lymphoblastic leukaemia (ALL) which occurs in 1-2% of cases of childhood ALL. The overt leukemia usually develops within 3-9 months of the apparent bone marrow failure. The neutropenia is usually more pronounced than the thrombocytopenia and sometimes there is an increase in reticulin within the hypocellular bone marrow. Inherited bone marrow failure disorders should also be excluded, such as Fanconi anemia, Dyskeratosis Congenita, Congenital Amegakaryocytic Thrombocytopenia in aplastic phase, Diamond-Blackfan anemia, and Schwachman-Diamond syndrome. Classical paroxysmal nocturnal hemoglobinuria (PNH), hypoplastic myelodysplastic syndrome (MDS), medications and infection should be ruled out also. This may be difficult as patients with AA can present with PNH clones; when the clone is smaller than % the diagnosis will be PNH in the context of bone marrow failure syndromes and the treatment will be those of AA. In case of larger clones the patient will be diagnosed as having PNH and treated as such. Differentiating between AA and hypoplastic MDS may be difficult, particularly when clonal cytogenetic markers are absent. Transient chromosomal abnormalities may be present in AA and may reflect oligoclonality of the stem cell compartment, whereas true clonal expansions are of prognostic significance. Monosomy 7 is the most frequent cytogenetic abnormality observed during such evolution and is associated with a poor prognosis. This evolution is most often associated with persistence of low counts or further worsening of cytopenia. SNP- or CGH-array–based cytogenetics may be helpful in

distinguishing AA from hypoplastic MDS and/or in the early detection of clonal progression.

Supportive care

Provision of information and psychological support to parents and children is of utmost importance. Preventive measures should be taken to avoid infection and bleeding, such as reversed isolation and selective gut decontamination with preferably non-absorbable antibiotic and antifungal drugs including cotrimoxazol which prevents Pneumocystis carinii infection as well. Medical care continues to depend upon meticulous attention to issues of infection and hemorrhagic diathesis and expectant management of regimen-related toxicities. In case of neutropenic fever, empiric broad spectrum antibiotics should be started after taking blood cultures. When fever persists without known cause for more than two days after initiation of antibiotics, antifungal therapy should be added. Prophylactic platelet transfusions should be given when the platelet count is $<10 \times 10^9$/l (or $< 20 \times 10^9$/l in the presence of fever).

Management of infection should be initiated before giving immunosuppressive therapy or proceeding with HSCT, although it may sometimes be necessary to proceed straight to transplantation in the presence of severe infection as it may offer the best chance of early neutrophil recovery.

Red blood cells should be given in case of anemia (Hb <4.5 mmol/l, or <5.5 mmol/l in case of anemic problems) and platelet concentrates in case of thrombocytopenic bleeding. Pre-storage leuko-reduction/-depletion of red blood cell and platelet concentrates to prevent HLA-alloimmunisation should be used for every patient with AA. Irradiation of blood products is current praxis to prevent transfusion-associated GvHD and to reduce sensitization to HLA and non-HLA antigens from multiple transfusions in patients who are candidates for transplant and for ATG treatment, during and after these treatments, until the lymphocyte count recovers $>1.0 \times 10^9$/l.

Transfusion of irradiated granulocyte transfusions may be considered in patients with life-threatening neutropenic sepsis.

A short course of G-CSF may be considered for severe systemic infection that is not responding to intravenous antibiotics and anti-fungal drugs, but should be discontinued after one week if there is no increase in the neutrophil count.

Iron chelation therapy should be considered when the serum ferritin is >1000µg/l. Expectant, cautious management is urged in regard to renal impairment, especially if there is concomitant use of renal toxic immunosuppressive drugs. Daily chelation with oral deferasirox has been studied prospectively in a large number of aplastic anemia patients with iron overload. Treatment was well tolerated and effective in decreasing serum ferritin and transaminases. In addition to producing desired improvements in organ function in a few cases, chelation with either deferasirox or deferoxamine has also intriguingly been associated with significant hematologic improvement. The routine use of rHuEpo in aplastic anemia is not recommended. Prednisolone alone should not be used to treat children patients with aplastic anemia because it is ineffective and encourages bacterial and fungal infection.

Definitive Treatment

Hematological stem cell transplantation (HSCT) and immunosuppressive therapy (IST) are the main treatment options for children with AA, of which HSCT is the only curative one. This makes HSCT the recommended first-line therapy when an HLA-matched sibling donor is available, although short - and middle term treatment outcomes of both modalities do not differ that much.

Since AA is a rare disease, it is most important either to centralize treatment or, second-best, to follow treatment protocols of (inter)national groups specialized in treatment of bone marrow failure syndromes, such as the Working Party Severe Aplastic Anemia of the European Blood and Marrow Transplantation group (EBMT).

Matched sibling HSCT

HSCT with an HLA-identical sibling donor is the initial treatment for newly diagnosed children with severe or very severe aplastic anemia. Pediatric survival rates after matched sibling HSCT for SAA are excellent, 90% and even higher in some series.

The mainstay of conditioning is cyclophosphamide with or without additional agents, but there is no indication for irradiation in the regimen for HLA-identical sibling transplantation. Children with SAA remain at increased risk for late graft rejection, and immunosuppressive agents used for GVHD prophylaxis post-transplantation should be weaned with great caution.

The recommended source of stem cells for transplantation in AA is bone marrow.
Pediatric reports of peripheral blood stem cell transplantations (PBSCT) describe rapid engraftment and increased chronic GVHD. The improved survival upon PBSCT seen in some adult studies does not carry over to the pediatric population, however. Schrezenmeier et al reviewed outcomes of almost 700 patients undergoing HLA-matched sibling BMT for SAA and found that in patients under age 20 years, significantly increased mortality and chronic GVHD was associated with PBSC transplantation.

Immunosuppressive therapy

For patients with (very) severe AA lacking a matched sibling donor or with non-severe AA who are transfusion-dependent IST is indicated. The multi-agent regimen of ATG (especially with horse derived preparation) and CsA (generally accompanied by a brief course of corticosteroids) is the standard immunosuppressive regimen. Substantial data as to the relative efficacy of the preparations have shown the superior effect of the horse ATG. Cyclosporin should be continued for at least 12 months after achieving maximal hematological response, followed by a very slow tapering, to reduce the risk of relapse. The routine use of long term G-CSF, or other hematopoietic growth factors is

not recommended. Response rates to IST in children are favorable, with survival ranging from 68% in one institution to 80% in another retrospective study at 10 years, with 89% survival if the analysis is confined to responders to IST. There are data demonstrating the risk for malignant evolution over time with IST therapy, with rates of myelodysplastic syndrome / acute myelogenous leukemia ranging from 8% to 25%.

Modifications to the conventional IST regimen, including addition of danazol, mycophenolate mofetil, sirolimus or hematopoietic growth factors have not significantly improved response or decreased relapse rates. Such agents currently have no place in primary therapy, although a few studies suggest that the addition of danazol or growth factors has altered relapse rates. Very little information is available about the substitution of tacrolimus for CsA. Alternative immunosuppressive regimens, such as alemtuzumab with or without CsA also show promise.

For children refractory to IST or who relapse after successful IST, evolution to MDS, AML or PNH should be ruled out first. In case of real refractoriness or relapse treatment with an additional course of ATG-based IST is possible; however, HSCT with a MUD donor has become a preferred option. Results of a second course of IST are generally disappointing, with only a 30% overall response rate. A prospective trial in 52 pediatric patients failing initial IST compared a second course of IST with unrelated donor HSCT and found an 11% response rate to IST with a 5-year failure-free survival rate of 9.5% in the former group, compared with an 84% 5-year failure-free survival rate in the latter group. Moreover, a higher risk of clonal evolution over time is associated with repeat IST.

Alternative donor HSCT

The above choice is heavily influenced by the recent significant improvement in the outcome of alternative donor transplantation, using either matched or mismatched unrelated donors or mismatched related donors. Four year survival data for unrelated transplants equal those of identical sibling transplant. In a multivariate analysis of the

European registry data, in which actuarial survival after alternative donor HSCT improved from 38% to 65% in the periods 1991-1996 and 1997-2002, respectively, only year of transplantation was associated with increased survival. It is likely that progressive changes in dimensions such as improved performance status, decreased number of prior transfusions, decreased interval from diagnosis to transplantation, improved supportive care, better donor-recipient matching, and use of less-intensive (particularly low-dose radiation or radiation-free) regimens contributed to this association and to the improved results in other recent studies. Stem cell source should be preferably bone marrow.

Overall better-matched patients have superior outcomes after alternative donor HSCT in pediatric patients. The optimal conditioning regimen for MUD HSCT is uncertain, but currently a Fludarabine, non-irradiation-based regimen is favored for pediatric patients less than 14 year of age, whereas for patients older than 14 years of age low-dose TBI is added. The preparative regimen included Fludarabine, Cyclophosphamide, and ATG with CsA and MTX for GVHD prophylaxis.

Follow-up

Patients with AA should be followed life-long: after IST because of the risk on malignant evolution of the bone marrow, after HSCT on a solid tumor and other common transplant-related late effects.

Patients undergoing HSCT for acquired AA are at significant risk for malignancy, most commonly carcinoma of the skin and oral mucosa. Major risk factors that have been identified are the development of chronic GVHD and the use of radiation-based conditioning regimens. Children who receive non–TBI-containing transplantation regimens for acquired AA demonstrate normal growth, with attainment of final adult height close to that predicted from parental height, normal thyroid and adrenal function, and preserved fertility. Regardless of the preparative regimen used, all patients undergoing HSCT should receive routine monitoring of growth and development,

endocrine and pulmonary function, and bone marrow density, and patients receiving radiation-containing regimens should receive fertility counseling as well before proceeding to transplant to offer fertility preserving measures if possible.

Treatment Algorithm

A - Matched related family donor allogeneic HSCT:

Indications:

1. Severe and very severe AA as the first line therapy.
2. Transfusion dependent non-severe AA after failure of first line immunosuppressive therapy (IST-1).

Conditioning regimen: CY/ATG: Cyclophosphamide 50 mg/kg BW daily for 4 days and ATG (either horse ATG at 30 mg/kg BW daily for 5 days, or rabbit ATG at 2.5 mg/kg BW daily for 4 days).

Stem cell source: bone marrow.

GVHD prophylaxis: CsA and short course of MTX (10 mg/m^2 at day +1, +3 and +6). Continue full dose of CsA (trough level between 100-200 ng/ml up to 9 months, then taper off in three months and stop it at 1 year post transplant if there is no GVHD.

B - Immunosuppressive therapy (IST): ATG/CSA

Indications:

1. Severe and very severe AA for patients without a matched related family donor.
2. Transfusion dependent non-severe AA.

Treatment scheme: exactly the same as for adults. See section xxx please.

C - Matched unrelated or cord blood HSCT:

Indications:

1. Very severe and severe AA after failure (no response or relapse) of IST-1.
2. Transfusion dependent non-severe AA after failure (no response or relapse) of IST-1 and 2.

Conditioning regimen: Fludarabine 30 mg/m^2/day for 5 days (day -7 to-3); Cyclophosphamide 50 mg/kg BW daily for 4 days (day -5 to -2) and ATG (either horse ATG at 30 mg/kg BW/day or rabbit ATG at 2.5 mg/kg BW/day for 4 days (day -5 to -2).

Stem cell source: bone marrow as first choice, peripheral blood or cord blood as second choice.

GVHD prophylaxis: CsA and short course of MTX (10 mg/m^2 at day +1, +3 and +6) for MUD; CsA, MMF for UCBT. Continue full dose of CsA (trough level between 100-200 ng/ml) up to 9 months, then taper off in three months and stop it at 1 year post transplant if there is no GVHD.

D - Haplo-identical HSCT:

Indications:

1. Rescue for primary graft failure following unrelated cord blood transplantation.
2. Patients failing IST1 and 2 and having no available related, unrelated or cord blood donor.
3. Patients in need of urgent recovery of neutrophils for whom no other stem cell donor will be available in due time.

Conditioning regimen: Fludarabine 30 mg/m^2/day for 5 days (day -7 to-3); Cyclophosphamide 50 mg/kg BW daily for 4 days (day -5 to -2) and rabbit ATG at 2.5 mg/kg BW daily for 4 days (day -5 to -2).

Stem cell dose: Bone marrow CD34+ selection by Clinimacs to reach 6-8 x 10^6 CD34+ cells/kg patient body weight, with a maximum of CD3+ cells of 5 x 10^4/kg patient body weight, or peripheral blood CD34+ selection to reach ....

Graft versus host prophylaxis: with CsA (MTX is not needed); in case of a CD34+ selected graft no GVHD prophylaxis at all.

Unrelated donor search in pediatric patients.
URD search should be initiated at primary work up and decision making for IST when it is clear that a matched sibling donor is not available. If a search prognosis indicates that a MUD will be found easily, it is reasonable to wait with a complete search until it is clear that a transplant has to be done at evaluation at 3 months after the start of IST.

But remember: Bone marrow failure is a medical emergency, thus IST should immediately be started after the second diagnostic bone marrow if no matched sibling donor is available.

Hierarchy of donor preferences in alternative donor HSCT should be as follows:

1. MUD
2. 1 Ag m/m MUD
3. depending on the centers experience: matched or minimally m/m cord blood,or haploidentical donor.

Summary

Incremental gains have been made in both the diagnosis and management of aplastic anemia. Greater understanding of regimen-related toxicities, either acute or delayed and potentially chronic, provides an impetus for the improvement of therapeutic strategies.

Matched-sibling HSCT is the treatment of choice with excellent results. Current immunosuppressive treatment (IST) induces durable remissions in 70%-80% of patients with aplastic anemia (AA) and results in 70 % long-term survival. In recent years, the survival of refractory patients has also improved. Apart from relapse and refractoriness

to IST, evolution of clonal diseases, including PNH and MDS, are the most serious long-term complications and constitute a strong argument for definitive therapy with HSCT if possible. Consequently, the detection of diagnostic chromosomal abnormalities (mostly monosomy 7) is of great clinical importance. Alternative donor HSCT surely has gained a firm place in the treatment of children with AA.

Abbreviations used

AA – Aplastic Anemia
ALL – Acute Lymphoblastic Leukemia
ATG – Anti Thymocyte Globuline
BM – Bone Marrow
BMF – Bone Marrow Failure
CsA – Ciclosporine-A
GVHD – Graft Versus Host Disease
HSCT – Hematopoietic Stem Cell Transplantation
IST – Immunosuppressive Therapy
MDS – Myelodysplastic syndrome
MUD – Matched Unrelated Donor
PBSCT – Peripheral Blood Stem Cell Transplantation
PNH – Paroxysmal Nocturnal Hemoglobinuria

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