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Aplastic Anemia - Diagnostics and Therapy of Acquired Aplastic Anemia

Recommendations from the society for diagnosis and therapy of haematological and oncological diseases

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Aplastic Anemia - Diagnostics and Therapy of Acquired Aplastic Anemia

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- Guideline
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1 Definition and Basic Information

The term **aplastic anemia (AA)** (synonyms: panmyelopathy, panmyelophthisis) comprises a group of pathogenetically heterogeneous bone marrow failures. They are characterized by a bi- or tricytopenia (anemia, granulocytopenia, thrombocytopenia occurring in various combinations) which arises from hemopoietic failure due to hypoplasia or aplasia of the bone marrow [1].

Bone marrow failures due to the exposure of ionizing radiation or myelotoxic substances are not referred to as aplastic anemia. Likewise, aplastic anemia must be strictly distinguished from the isolated aplastic anemia (PRCA, “pure red cell aplasia”). The latter becomes manifest in one cell line only, however, differs in pathogenesis and therapeutic approach.

The incidence rate of AA in central Europe amounts to approx. 2–3/10^6/year. An acquired aplastic anemia might appear at any age in life. The age distribution of the disease shows two peaks, one between 10 and 25 years, and a second among the over 60 year-olds. There is no sex predilection.

2 Classification

Classification of AA is based on blood cell counts and reveals three subgroups:

- moderate aplastic anemia = MAA or **nSAA** (“non-severe AA”)
- severe aplastic anemia = **SAA**
- very severe aplastic anemia = **vSAA**

Threshold values are summarized in Table 1 (two out of three blood criteria must be fulfilled).

Table 1: Classification of Aplastic Anemia (two out of three criteria must be fulfilled)

	nSAA	***SAA***	***vSAA***
Neutrophils	< 1.0 G/L	< 0.5 G/L	< 0.2 G/L *
Platelets	< 50 G/L	< 20 G/L	< 20 G/L
Reticulocytes	< 20 G/L	< 20 G/L	< 20 G/L

Legend:
** For vSAA classification the granulocyte criterion < 0.2 G/L must be fulfilled.*

This classification is of prognostic relevance and has an influence on therapeutic procedures (see Chapter 5).

Another classification is based on the presumed etiology [2]:

- Idiopathic (> 80 %)
- Drug-induced (< 20 %)
- Post-infectious (particularly after hepatitis due to a hitherto unidentified pathogen (< 5 %) [3]
- Hereditary forms with initial manifestation at adult age (late onset hereditary bone marrow failure syndromes), e.g. in the scope of a congenital dyskeratosis or related telomeropathies and/or in connection with homozygous thrombopoetin receptor (MPL) mutations (< 1 %) [4, 5].

The prognostic and/or therapeutic relevance of this classification has not been corroborated. One exception is the drug-induced aplastic anemia. If AA is suspected to have been induced by drugs, therapy with the drugs in question should be terminated and re-exposure prevented for the rest of the patient's life. Drugs proved or at least suspected to induce AA are, among others, anti-inflammatory substances (gold, pencillamines, phenylbutazone, diclofenac, indomethacin), anticonvulsant drugs (phenytoin, carbamazepine), thyreostatic drugs (carbimazole, thiouracil), antidiabetic drugs (tolbutamide), antimalarial agents (chloroquine), antibiotics (sulfonamides, cotrimoxazole, chloramphenicol) (for a detailed review please refer to the specialized literature [2, 6].

3 Clinical Presentation

Symptoms of aplastic anemia result from the bi- /tri-cytopenia [1]:

- Anemia
- Neutropenic Infection (oral cavity and pharyngeal ulcers,
- necrotizing gingivitis or tonsillitis, pneumonia, phlegmon)
- Bleeding of the thrombocytopenic type.

Because of constitutional forms (congenital dyskeratosis and related forms) attention should be paid especially to pigment anomalies on the skin, leukoplakias in the oral mucosa, dystrophies of finger and toe nails, dyskeratoses as well as clinical signs of pulmonary fibrosis or hepatic cirrhosis [7].

Lymphadenopathy, hepatomegaly and splenomegaly speak against an aplastic anemia. Differential blood cell counts reveal a bicytopenia, however, in most cases a tricytopenia, of various extent.

4 Diagnosis

4.1 Evidence of Diagnosis

Table 2 summarizes the criteria for diagnosis.

Table 2: Criteria for the Diagnosis of Aplastic Anemia

Parameter	Description	Comments
Differential Blood Cell Count	Bi-/tricytopenia	Anemia is often normocytic /normochromic, occasionally moderately macrocytic and with inconspicuous erythrocyte morphology Leukocytopenia resulting from granulocytopenia and monocytopenia, often no immature granulocytic precursor cells in the blood Absence of giant platelets in blood smears
Bone Marrow	Aplasia or hypoplasia Cellularity < 25 % No infiltration of neoplastic cells Without fibrosis	Bone marrow aspirate and bone marrow biopsy are mandatory Biopsy length at least 15mm Not unusual: focal decrease in medullary density, “spot-like pan-myelopathy”

4.2 Differential Diagnostics and Diagnosis by Exclusion

Hypoplastic acute leukemia, (hypoplastic) myelodysplastic syndrome, hairy cell leukemia and other lymphomas, bone marrow infiltration by solid tumors, osteomyelofibrosis, hypersplenism, severe megaloblastic anemia, anorexia nervosa, systemic lupus erythematodes, paroxysmal nocturnal hemoglobinuria, Fanconi anemia, congenital dyskeratosis, Shwachman-Diamond syndrome, isolated aplastic anemia ("pure red cell aplasia"); aplasia after chemotherapy or radiation therapy.

4.3 Diagnostics

4.3.1 Initial Diagnostics

The diagnostic measures upon initial diagnoses serve the purpose of corroborating the diagnosis, clarifying the etiology, the severity grade, and the prognosis:

- Detailed medical drug therapy history
- Clinical examination. Attention should be paid particularly to the following aspects which are relevant as clinical signs of cytopenic complications or as information for differential diagnostics: infection, signs of bleeding, jaundice, splenomegaly, hepatomegaly, lymphadenopathy, nail dystrophies, leukoplakias, pigment anomalies, skeletal anomalies, dental anomalies, short stature.
- Cell counts, differential blood cell count, reticulocytes twice
- Bone marrow diagnostics: Aspirate with cytology, iron stain, bone marrow histology (at least 15mm biopsy length), cytogenetics;
- Optional: assays for colony-forming cells derived from bone marrow
- Flow cytometric analysis of GPI-anchored proteins on granulocytes and erythrocytes, if possible, on reticulocytes and monocytes (see also Guideline Paroxysmal Nocturnal Hemoglobinuria)
- Hemolysis parameters: LDH, haptoglobin, bilirubin, perhaps hemosiderin in the blood
- Telomeric length measurement (e.g. by means of the Flow-FISH method; in case of shortened telomeric length below the 10th percentile of an age-equivalent control group: mutation analysis of TERT, hTERC, TIN2, if possible, further components of telomerase complex [8, 9, 10])
- Coagulation: Quick’s value, PTT, fibrinogen
- CRP
- Total protein, electrophoresis, GOT/GPT, AP, creatinine, uric acid, blood glucose
- Ferritin

- Vitamin B12, folic acid
- Antinuclear antibodies, anti-DNA antibodies
- Immunoglobulins
- Blood group, direct antiglobulin test
- X-rays of the chest, sonography of the abdomen
- EBV, CMV, hepatitis A, hepatitis B, hepatitis C, HIV, Parvovirus B19

4.3.2 Only in Case of Special Indication

- Only in case of stem cell transplantation candidates: HLA class I and II typing
- In case of insufficient increase in the number of platelets under platelet substitution:
- HLA-A and HLA-B typing for the selection of HLA-matching platelet donors.
- If DD Fanconi anemia: chromosome fragmentation test or cell-cycle analysis; if possible, mutation analysis of the Fanconi anemia genes.
- In case of clinical signs of congenital dyskeratosis: determination of the length of telomeres and mutation analysis of the DKC1 gene, if possible, also other genes belonging to the telomerase complex.

More recent studies demonstrated that a relevant proportion of patients with a presumably acquired aplastic anemia actually had a late-onset form of congenital bone marrow failure. The broad application of screening tests (chromosome breakage and telomeric length determination) and targeted molecular diagnostics are recommended particularly for adolescents and young adults [11].

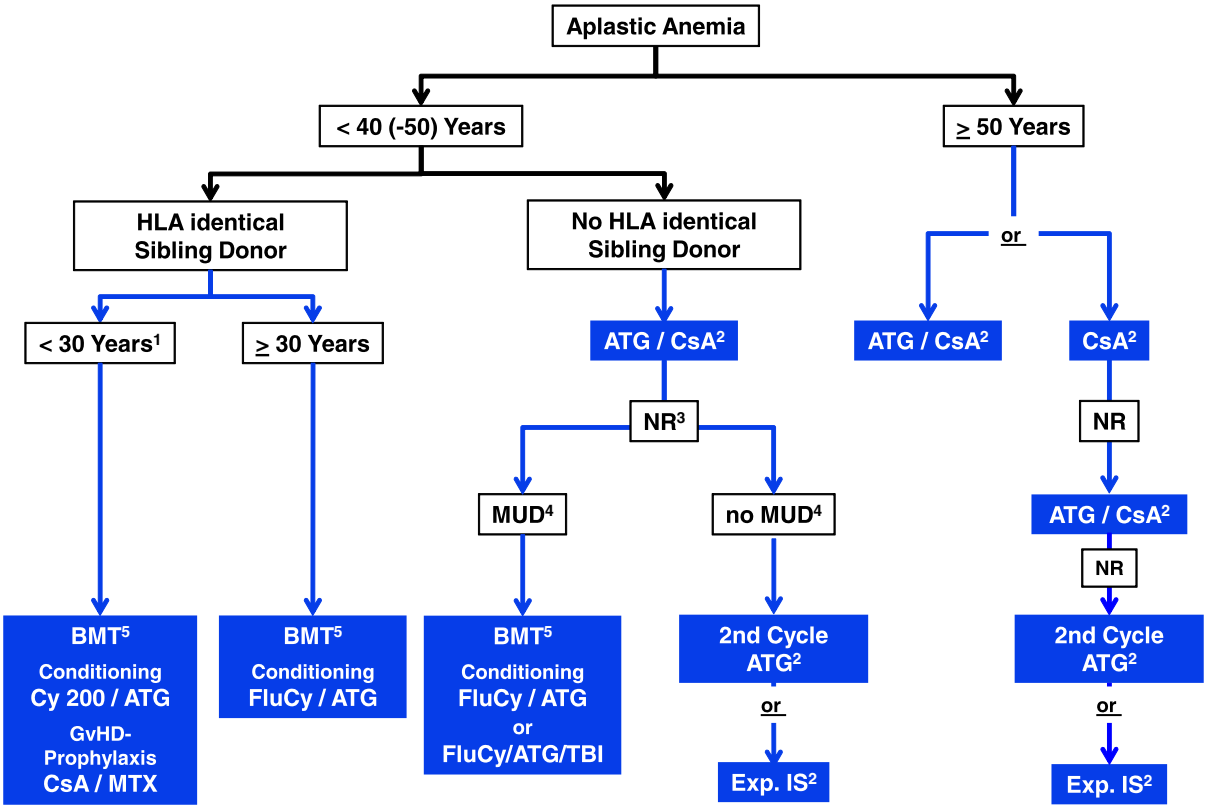
5 Therapy

5.1 Object of Therapy

Induction of a “remission” and thus prevention of bleeding complications and neutropenic infections, as well as prevention of chronic transfusion requirement (iron overload; allosensitization).

A therapy algorithm for first-line therapy is shown in Figure 1.

Figure 1: Therapeutic Procedure Algorithm in Cases of Acquired Aplastic Anemia in Adults



Legend:

[1] As for children, please refer to the Protocols and Guidelines of the Pediatric Aplastic Anemia Study Group;

[2] Therapy: ATG – antithymocyte globulin, CsA - ciclosporin A; this therapy algorithm is based on studies which have been conducted with horse –ATG, the use of which is also recommended in routine therapy outside of studies, see Chapter 5.6.2); IS – experimental immunosuppressive therapy;

[3] NR – Non-responder;

[4] MUD – Matched Unrelated Donor ;

[5] BMT: Cy200 - cyclophosphamide 200 mg/kg, FluCy/ATG – fludarabine, low-dosed cyclophosphamide and ATG, BMT – bone marrow transplantation, MTX – methotrexate, TBI - total body irradiation

5.2 Therapy Planning

The choice of therapy depends on the severity of the disease, the age of the patient, and the degree of HLA-identity in a potential related or unrelated bone marrow donor, Figure 1. Studies confirm that particularly in case of bone marrow transplantations, the interval between diagnosis and therapy has a significant influence on the prognosis [12]. Consequently, a sound tentative diagnosis should be reason enough to refer patients to a Hematological Center which has experience in the therapy of aplastic anemia.

5.3 Indication for Therapy

Therapy will be indicated in patients with symptomatic, therapy requiring or high risk disease:

- Invariably in severe cases of aplastic anemia according to definition (SAA and vSAA)
- nSAA with severe cytopenia of at least one cell line which requires regular transfusions or with an increased risk for infections or bleeding; in other situations the individual case is to be assessed, also taking into special consideration the course of the disease.
- Progression of nSAA into SAA

5.4 Supportive Therapy

The overall survival after immunosuppressive therapy of AA has continually improved during the last 30 years [13]. However, this not only applies to patients who respond to the therapy of the basic disease with a reconstitution of hematopoiesis, but also to patients who fail to respond [14]. This shows the significance of supportive therapy for overall survival. Relevant elements prophylaxis and treatment of infections, a restrictive transfusion strategy, and the therapy of an iron overload. In detail, the following aspects of supportive therapy must be observed.

5.4.1 Infection Prophylaxis

- Reverse isolation, air filtration, prophylactic antibiotics and antimycotics for all patients under antithymocyte globulin therapy (ATG) and suffering severe neutropenia [15].

Fluochinolones should be preferentially applied as prophylactic antibiotics, alternatively to antibiotics that are not resorbable [15, 16].

Fluconazole, itraconazole, or posaconazole are recommended for antimycotic prophylaxis [17].

(Comment: The recommendations are based on the examination of neutropenic patients in the context of malignant diseases and chemotherapy [16, 17, 18, 19, 20, 21] and were transferred to AA patients; there are no meaningful studies dealing with the effect of the abovementioned measures on the rate of infection and infection-dependent mortality that apply specifically to patients with AA [15].

There is no indication for prophylaxis against *Pneumocystis jirovecii* or cytomegaloviruses (exception: alemtuzumab therapy; see below) [15].

5.4.2 Bleeging Prophylaxis

- Menolysis.
- Strict avoidance of any kind of platelet aggregation inhibitor.
- In cases of severe thrombocytopenia and clinically relevant hemorrhages perhaps the application of tranexamic acid, especially if the increment after platelet substitution is insufficient.
- In case of therapy with ciclosporin interactions with other drugs should be observed.
- Platelet transfusion (see Chapter 5. 4. 3.).

5.4.3 Transfusions

- In many patients transfusions are necessary to ascertain a sufficient physical resistance and quality of life, and to prevent complications due to hemorrhages. On the other hand, frequent erythrocyte transfusions might result in the alloimmunization against erythrocytic antigens and iron overload. Platelet transfusions are capable of inducing an immunization against HLA and HPA antigens. Earlier studies (before the introduction of leukocyte depletion) revealed a negative correlation between the number of transfusions prior to allogeneic stem cell transplantation and survival [22, 23, 24]. It is uncertain whether this correlation is still valid [26], considering the efficiently leukocyte-depleted products which display a low rate of alloimmunization [25]. A restrictive transfusion strategy is to be recommended nevertheless. It should focus on the symptoms (anemia symptoms, potentially hazardous spontaneous bleeding) [27].

- The transfusion of leukocyte-depleted blood products is mandatory in AA patients [27]. In Germany, however, this does not require any specific selection to be made by the treating physician, as only leukocyte-depleted cellular products have been allowed to be marketed since 2001 (< $1.0x10^6$ leukocytes/unit) [27].
- Erythrocyte concentrates should be transfused in case of signs of hypoxic anemia. The indication for transfusion must depend on the objective stress capacity, subjective symptoms and comorbidity [28].
- In stable out-patients without accompanying risks, which increase the hazard of hemorrhages (e.g. fever, infections) platelets should be transfused prophylactically below the threshold of 5,000/µl [28, 29]. This low transfusion trigger requires regular blood cell counts (at least once per week), the absence of signs of bleeding, and the possibility of rapid transfusion once signs of bleeding occur. In patients with fever >38°C, infections, signs of bleeding, or patients with a case history which contains severe hemorrhages (WHO grade 3 or 4), and in cases of alloimmunization, the transfusion trigger should be adjusted to 20,000 /µl [28].
- Immediate transfusion is required in patients with hemorrhages of grade 3 or grade 4.
- Many patients have a stable 'individual' threshold below which severe signs of bleeding will appear. This threshold value individual to the patient is to be integrated into the overall concept especially when a severe bleeding of grade 3 or grade 4 had already occurred once before in patient with a platelet value of > 5,000 / µl [30].
- In patients with ATG therapy, the platelet value should be increased to 50,000 /µl prior to the onset of ATG infusions, as a rapid drop of platelets might ensue under ATG infusion.
- Platelet transfusion should be done prior to invasive interventions in order to reach the thresholds values respectively recommended [28].
- The restrictive transfusion strategy applies especially to patients scheduled for allogeneic stem cell transplantation [22, 23, 24]. Never should blood products derived from relatives be applied in targeted transfusions.
- The application of granulocyte concentrates might be considered as a temporary measure in case of life-threatening infections and severe neutropenia [31].
- The irradiation of blood products for patients with aplastic anemia may be performed because of two indications: (i) prevention of a transfusions-associated GvHD, and (ii) prevention of an allosensitization [32, 33]. In order to prevent a transfusion-associated GvHD an indication to irradiate blood products with 30 Gy exists in the following situations:
    - While ATG therapy is in progress and until reconstitution of the lymphocyte count to at least $1x10^9$/L all blood products must be irradiated [28, 32].
    - In case of other intensive immunosuppressive therapies (e.g. fludarabine) [28].
    - Patients who receive an allogeneic stem cell transplantation, starting at the latest when conditioning is initiated [28].
    - Some centers give irradiated blood products to all their patients with an AA diagnosis regardless of the therapeutic context in order to prevent alloimmunization [32, 33].
    - HLA-selected platelet apheresis donations [29]
    - Granulocyte concentrates [29]

5.4.4 Iron Chelation

In cases of AA there is the hazard of transfusion-dependent iron overload, particularly in patients who do not respond to immunosuppression and must receive transfusions over a longer period of time. Normally ferritin or hepatic iron values requiring an immediate chelate therapy will not be reached in the first months after the diagnosis. A period of at least 4-6 months should be waited after induction of immunosupression. When remission is achieved an iron overload can be treated with blood-lettings. Chelate therapy is recommended in case regular transfusions become a persistent requirement when serum ferritin levels exceed 1,000 ng/ml [13]. This applies especially also to transfusion candidates, as an iron overload is associated with s higher transplantation-related mortality and a worse rate of survival [34, 35, 36, 37]. No drug-induced cytopenias were observed in a study including 116 AA patients with an iron overload who received deferasirox; the serum ferritin levels decreased markedly within one-year therapy [38].

5.5 Allogeneic Stem Cell Transplantation

5.5.1 Allogeneic Stem Cell Transplantation from an HLA-Matching Sibling

An indication for an allogeneic bone marrow transplantation from an HLA-identical sibling donor exists in the following situations:

- As primary therapy [13, 39, 40]:
  - In cases of severe or very severe aplastic anemia and age < 40 years;
  - In cases of very severe aplastic anemia (vSAA) perhaps also in older patients, depending on the clinical overall assessment.
- As secondary therapy [13, 39, 40]: In cases of SAA and age < 50 years after the failure of at least one cycle of immunosuppressive combination therapy with horse-ATG and ciclosporin A (see below).

5.5.1.1 Stem Cell Source

In cases of aplastic anemia bone marrow should be used as the source for stem cells, as transplantation with peripheral blood stem cells (PBSZ) is associated with a significantly higher incidence rate of acute GvHD, severe chronic GvHD, and a significantly worse rate of survival [41, 42].

5.5.1.2 Conditioning

In case of sibling donor transplantations in young patients (≤ 30 yeas) cyclophosphamide (total dose of 200mg/kg b.w. distributed in four administrations on consecutive days) is the standard conditioning regime [13, 39, 40]. It is controversial whether the supplemental administration of ATG is an advantage. A randomized study failed to reveal a significant influence of ATG on rejection, the incidence of severe acute GvHD or total survival [43]. However, analyses of single centers and retrospective analysis of the EBMT demonstrated a significantly better survival with ATG in conditioning [13]. A total or partial body irradiation in the scope of conditioning is not indicated for a sibling donor transplantation.

Prognostic variables essential to survival after transplantations among siblings are age, performance status, the interval between diagnosis and transplantation as well as the source of the stem cells [12, 13, 34, 35]. As the likelihood of survival decreases with age, which is particularly

evident among patients older than 30, [12, 13], new conditioning protocols were studied with respect to this age group. A pilot study revealed that a combination of low-dosed cyclophosphamide, fludarabine and ATG produced good results in patients who were older than 30 years [44] and is being evaluated in a study of the EBMT Aplastic Anemia Working Party (www.ebmt.org). In this combination of low-dosed cyclophosphamide and fludarabine alemtuzumab may be an alternative to ATG [45].

5.5.1.3 GvHD Prophylaxis

The standard regime for GvHD prophylaxis is the combination of ciclosporin und methotrexate.

A randomized study compared GvHD prophylaxis done with ciclosporin alone (onset on Day -1) with ciclosporin (onset on Day -1) and methotrexate (15 mg/m^2 on Day +1 and 10 mg/m^2 on Day +3, +6 and +10). The combination therapy CsA + MTX was associated with a significant advantage in survival and is considered to be the standard of GvHD prophylaxis in cases of sibling donor transplantation because of AA [46, 47].

There is a high risk of late transplant failure after transplantation, especially in patients with an increasingly mixed chimerism [48]. Complete donor chimerism or a stable mixed chimerism is associated with a low rate of chronic GvHD and with a good survival rate [49]. There is an association between increasingly mixed chimerism and transplant rejection with the cessation of ciclosporin therapy. For this reason it is recommended to administer therapeutic doses of ciclosporin over a period of at least nine months and then gradually terminate therapy (at least over a period of three months) under surveillance of the chimerism status [41, 42].

5.5.2 Allogeneic Stem Cell Transplantation from an Unrelated Donor

The indication for an unrelated transplantation exists in the following situations:

- Primary therapy [13, 39, 40]: At present, there is no unambiguous agreement about the application of unrelated transplantation as primary therapy of acquired aplastic anemia. Good results obtained with modified conditioning regimes (see below) can justify the application of unrelated transplantation as primary therapy in young patients with vSAA, if a donor with a 10/10 match (minimum: 9/10 match) on the level of alleles is available [50, 51].
- Secondary therapy [13, 39, 40]: In case of SAA / vSAA and age ≤ 40 years after failure of at least one cycle of immunosuppressive combination therapy with horse -ATG and ciclosporin A (see below) and absent availability of an adequate sibling donor; perhaps also in patients > 40 years of age, if other therapy options are exhausted and a good “performance status” exists.

In case of patients who on account of age, performance status and severity grade of the disease come into question for an unrelated transplantation as second-line therapy the search for an unrelated donor should be initiated at an early stage.

5.5.2.1 Conditioning for Unrelated Stem Cell Transplantation

A dose-reduced conditioning regime which is modified relative to sibling donor translations should be applied in cases of unrelated transplantation. The EBMT recommends the combination of low-dosed cyclophosphamide (300 mg/m^2 on Day -6, -5, -4 and -3), Fludarabine (30 mg/m^2 on Day -6, -5, -4 and -3), ATG (on Day -6, -5, -4 und -3) or alemtuzumab [52, 53]. If patients are > 14 years old this regime has been adjusted as follows, because of the high rejection rate:

2Gy total body irradiation and administration of half of the ATG dose (only 2 days instead of 4 days) [52, 53].

Both ATG and alemtuzumab can be applied as T-cell antibodies in this regime [52, 53, 54].

According to this protocol ciclosporin A and methotrexate (10 mg/m^2 on Day 1 and 8 mg/m^2 on Day +3 und +6) are applied as GvHD prophylaxis .

An alternative approach consists in conventional cyclophosphamide conditioning (200 mg/kg) with ATG and low-dosed total body irradiation (2 Gy) [55, 56] or the combination of a reduced cyclophosphamide dose (120 mg/kg) and 8Gy-total body irradiation [57].

5.6 Immunosuppressive Therapy

5.6.1 Indication

An indication for immunosuppressive therapy exists in

- patients with vSAA or SAA > 40 (-50) years of age or in patients without HLA-matching sibling donor
- patients with nSAA with hazard because of severe cytopenia in at least one cell line

There is no age limit in immunosuppressive therapy [58, 59].

5.6.2 Triple Therapy with ATG, Ciclosporin and Corticosteroids as First-Line Therapy

The **standard therapy** outside of studies consists in the combination of horse -ATG, ciclosporin and corticosteroids [60, 61]. This combination therapy is superior to therapy with ATG or ciclosporin with regard to response rate and survival independent of therapy failure- — the same applies to nSAA [72]. The respective studies which established this triple combination as the gold standard were all conducted with horse-ATG [60, 61, 62, 63, 64, 65, 66, 67, 68, 69]. The only horse ATG product registered in Europe (Lymphoglobulin®) was withdrawn from the market in 2007 [70]. Combination therapies were then applied with rabbit-ATG. A recently published randomized study comparing rabbit-ATG (Thymoglobulin®) with horse-ATG (ATGAM®) that the response rate and total survival is significantly better with horse-ATG than is the case with rabbit-ATG [71]. The response rate after three months amounted to 62% with horse-ATG, as compared to only 33% in the rabbit group. Total survival rate amounting to85% was significantly better after horse-ATG than after a therapy based on rabbit-ATG (55%) [71]. Other, non-randomized studies which examined rabbit-ATG efficacy in first-line therapy produced to some extent discrepant results [72, 73, 74, 75, 76, 77, 78, 79]. Five of the seven studies also report of a worse rates of response and total survival with thymoglobulin as compared to historical controls [72, 74, 75, 76, 79]. The remaining studies revealed identical results obtained with ATG from horse and rabbit [77, 78]. None of the studies reported improved response rates in primary therapy with thymoglobulin.

The change from horse-ATG to rabbit ATG practiced in Germany from 2007 to the publication of the data quoted above was not evidence-based, instead was due to lacking availability. It should be attempted to continue to perform triple therapy with horse-ATG by purchasing it from abroad [63].

Based on recent experiences the purchase on time from abroad is possible in most cases. The product (ATGAM®) is not registered in Germany. According to the current state of knowledge a triple therapy with horse-ATG is the immunosuppressive therapy with the best response rate

and the best rate of therapy-independent survival. This option should therefore be given priority after giving the patient the pertinent information. It is advisable to clarify the takeover of expenses with the cost bearers.

The lack of horse-ATG availability should not result in abstaining from an indicated ATG therapy. The response rate of combination therapy is better than that of ciclosporin monotherapy [69].

Other immunosuppressive multiple combinations (e.g. mycophenolate or sirolimus) did not any produce any improvement of the response rate [63, 64]. A high rate of early relapses occurred when mycophenolate was applied instead of ciclosporin [63].

5.6.3 Drugs

Details as to the authorization status and dosages are compiled in the Appendices Drug Therapy– Protocols and Authorization Status.

The recommended doses of **ATG** greatly vary with the product (thymoglobulin 2.5 - 3.75 mg/kg b.w. and day, an 5 consecutive days; ATGAM 30mg/kg and day on 4 consecutive days) [71].

The administration of corticosteroids is required concomitant to ATG therapy (e.g. prednisolone, initially 1mg/kg b.w. IV prior to ATG infusion; after cessation of ATG therapy to be continued with 1mg/kg b.w. PO). Subsequently swift gradual dose reduction until Day 28, unless there are symptoms of serum disease. An individual adjustment of the corticosteroid dose depending on the severity and the duration of the symptoms is required in the event of allergic reactions to ATG or emergence of a serum disease [47].

Ciclosporin should be administered initially at a dose of 5mg/kg b.w. / day PO; then the dose is adapted to measured levels (whole blood concentration, trough levels: 150-250ng/ml) [47]. Ciclosporin should be continued at least for four months, thereafter further control of therapy depending on response and course. Numerous patients responded after four months, however, still display gradually increasing blood cell counts. In such cases ciclosporin should be continued until, as documented over a period of 6-8 weeks, no additional improvement of blood cell counts will occur. Then a slow (!) dose reduction may be initiated (dose reduction at a rate of 0.3mg/kg body weight and month). A more rapid dose reduction is associated with a higher risk of recidivation [80].

5.6.4 Hematopoietic Growth Factors

The administration of **G-CSF** in combination with the triple immunosuppression results in an accelerated increase in neutrophile granulocyte numbers, lesser infections, and short hospitalization periods [68]. The trilinear response, event-free survival, relapse rate, and total survival are not improved by the administration of G-CSF [61]. One study revealed a significantly lower relapse rate in the G-CSF group as compared to a triple immunosuppression group without G-CSF [81]. However, another clinical study failed to confirm this result [61]. The application of G-CSF in cases of aplastic anemia outside clinical studies is not recommended [13, 82].

5.6.5 Evaluation of Response, Course

Under therapy with ATG platelets should be measured daily, differential blood cell counts and anticoagulation parameters twice per week and, if possible, the ciclosporin level. Then, in the regeneration stage, differential blood cell counts should be determined in intervals of one to two weeks. Status checks, cell counts, differential blood picture once per month, bone marrow analysis annually or in case of remarkable blood picture modifications.

The response to immunosuppressive therapy occurs with a delay. In the median it takes 3-4 months [60, 61, 62, 63, 64, 65, 66, 67, 68, 69]. The success of therapy can usually be estimated after four months [83]. A complete normalization of peripheral blood values is often not achievable [84].

The relapse rate after successful therapy amounts to 30% - 40% [85, 86]. Patients have an elevated risk for the emergence of MDS, AML and clinically symptomatic PNH as well as solid tumors [87, 88, 89].

5.6.6 Repetition of ATG Therapy

A repetition of triple immunosuppression is possible. The chance of a second response is high in case of relapses [85, 90]. If initial therapy fails a second immunosuppressive course can be applied which might induce a response in 30-60% of the patients [90, 91, 92]. There is no unequivocal evidence stating that a change of the ATG product will improve the response rate of a repeated therapy [93]. However, changing to a product derived from another species is common when therapy is repeated. If rabbit-ATG was used in primary therapy, and if non-response to initial therapy is an indication for repeated therapy, a change to horse-ATG should be made (see above, data on overall better response rates with horse-ATG).

A direct prospective comparison of a second ATG cycle with unrelated transplantation in children who had not responded to the first ATG therapy displayed a response rate to ATG therapy of merely 11% and had a better likelihood to survive unrelated transplantation [94].

A third cycle might be reasonable in relapse patients. However, a third ATG therapy cycle is not advisable if patients failed to respond to two previous cycles, as the response rates will then be very low [95].

5.7 Second-Line Therapy

If first-line therapy with triple immunosuppression fails the following therapies come into question (see Figure 1):

- Stem cell transplantation from an HLA-identical sibling donor (see Section 7.1)
- Stem cell transplantation from an unrelated donor (see Section 7.2)
- Repetition of immunosuppressive triple therapy (if necessary, change of the ATG-product; see above)
- Alternative immunosuppression: Alemtuzumab [96, 97] or high-dose cyclophosphamide [67, 98]
- Androgen therapy, e.g. with danazol, is an alternative to patients with short telomeres: (< 1% of the age-adjusted telomere length) +/- underlying telomeropathy [99, 100], or to patients not eligible for immunosuppressive therapy and allogeneic stem cell transplantation [101, 102].

A randomized study revealed that alemtuzumab administered in primary therapy had produced a lower response rate than ATG [96]. However, response rates of 37%-48% were reported in patients with refractory disease [96].

The high-dose cyclophosphamide therapy is very controversial. Positive reports [103, 104] face a clinical study which had to be prematurely terminated because of too high toxicity in the high-dose cyclophosphamide arm [67, 98].

Patients who responded to at least on standard triple immunosuppression or relapsed, and are not unambiguously eligible for allogeneic stem cell transplantation should, at the latest, at this point in time be brought to a specializing center in order to include experimental immunosuppression protocols or transplantation protocols (haploidentical transplantation, umbilical cord blood transplantation [105] in decision-making. These protocols will usually be applied in Europe-wide collaborations on account of the rarity of the disease. Information about current EBMT therapy studies can be found at www.ebmt.org.

A European register of the EBMT (Working Party Aplastic Anemia) carries out analyses to optimize the therapy of this rare disease. It is recommended to participate in this register which collects patient data irrespective of a form of therapy.

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10 Active Studies

Studies of the EBMT Working Party on Aplastic Anemia are under www.ebmt.org

11 Drug Therapy – Protocols

- Aplastic Anemia - Systemic Therapy Protocols

13 Authorization Status

Zulassungsstatus von Medikamenten (Situation in Germany - in German only)

15 Links

www.aplastische-anaemie.de

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17 Disclosure of Potential Conflicts of Interest

according to the rules of the German Association of Hematology and Medical Oncology (*DGHO, Deutsche Gesellschaft für Hämatologie und Medizinische Onkologie*) and the recommendations of the AWMF (version dated April 23, 2010) and international recommendations.

The authors declare that they have no conflicts of interest.