REVIEW ARTICLE

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Aplastic Anemia

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APLASTIC ANEMIA IS A DISEASE WITH A LONG HISTORY. THE FIRST CASE description was published by Paul Ehrlich in 1888, the term "anemia aplastique" originated with Louis Henri Vaquez in 1904, and clinical features were described by Richard C. Cabot and other pathologists in the early 20th century. What was once a terrifying, mysterious disease, most often sudden in onset and occurring in young persons, can now be successfully treated in almost all patients. An understanding of the pathophysiology of aplastic anemia, gained in the research laboratory, has guided the development of effective therapies. Marrow failure syndromes have been linked to viral infection and environmental toxins, inherited and acquired genetic mutations, early events in leukemogenesis, and the hematopoiesis of normal aging.

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DEFINITIONS

The long history of aplastic anemia has resulted in confusing terminology. The term "anemia" derives from the early ability to measure red cells in a hematocrit. Most patients with aplastic anemia have pancytopenia, with decreased platelets, white cells, and erythrocytes. "Aplastic" refers to the failure of marrow to form blood, and hematopoietic failure is the end-organ effect of diverse pathophysiological mechanisms. Yet a seemingly "empty" bone marrow may be entirely capable of supporting normal hematopoiesis. Conversely, bone marrow failure can occur without low marrow cellularity, as in the myelodysplastic syndromes and paroxysmal nocturnal hemoglobinuria (PNH).

PATHOPHYSIOLOGICAL FEATURES

There are three main pathophysiological mechanisms that can lead to an "empty" bone marrow (Fig. 1).

DIRECT DAMAGE TO MARROW

Damage to the bone marrow occurs most often iatrogenically, from chemotherapy or radiation therapy. The effects are dose dependent and transient at conventional doses. Other organ systems are affected, and spontaneous recovery is expected. Benzene also impairs hematopoiesis, and industrial exposure to benzene figured prominently in the early literature on aplastic anemia. Benzene exposure is now a negligible risk factor, accounting for only a small fraction of cases of marrow failure in most countries.[1,2] However, in China, a country characterized by rapid industrialization and slower regulation, benzene remains a workplace toxin.[3,4] Dosage is critical; workers with less intense or less prolonged exposure to benzene appear to have milder cytopenias, and they recover after termination of the exposure. Marrow failure is a proximate effect, not a late consequence, of benzene exposure.

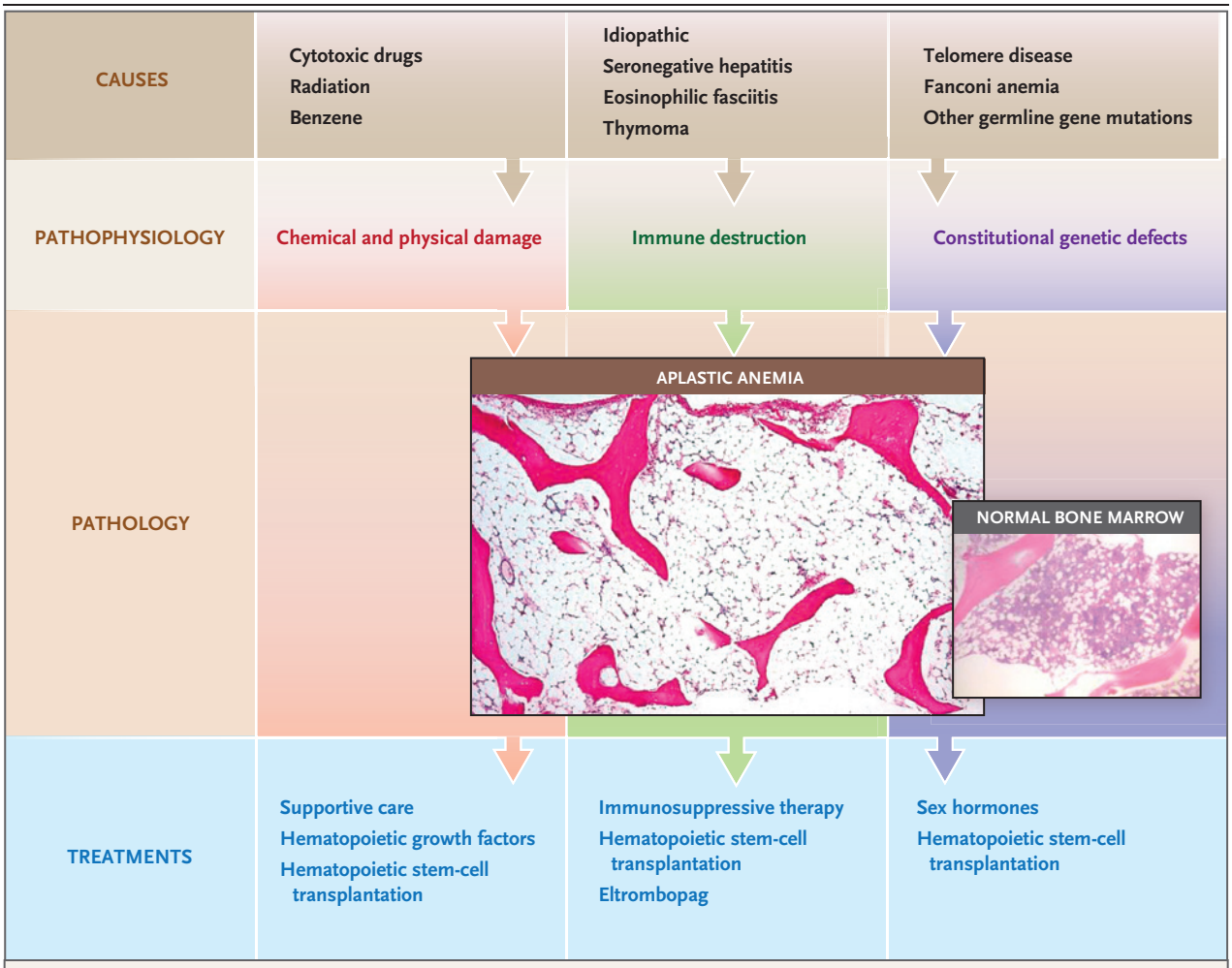

Figure 1. Diverse Pathophysiological Features that Lead to a Common Pathologic Process in Bone Marrow Failure.

Replacement of hematopoietic cells by fat is the distinctive pathologic feature of aplastic anemia. A hypocellular marrow can result from chemical or physical damage; the most frequent causes are iatrogenic, such as after cytotoxic chemotherapy or irradiation and exposure to benzene, usually in industry. In certain constitutional genetic defects that affect hematopoietic stem-cell function and the immune system, marrow failure and a hypocellular marrow are prominent. The disease immune aplastic anemia results from destruction, mainly by T cells, of hematopoietic stem cells and progenitor cells. Treatments are different for marrow damage, genetic defects that produce multiorgan effects, and the immune disease.

CONSTITUTIONAL SYNDROMES

Marrow failure results from specific loss-of-function germline mutations, usually inherited (Table 1 and Fig. 2A). There is a spectrum of genetic lesions that diminish the capacity for hematopoietic stem cells to repair DNA, as in Fanconi anemia (replication-dependent removal of interstrand DNA cross-links)[5] and dyskeratosis congenita (telomere maintenance and repair),[6] or interfere with differentiation and self-renewal pathways, as in *GATA2* deficiency.[7] Marrow failure also may occur in syndromes affecting immune regulation, such as in those due to cytotoxic T-lymphocyte–associated antigen 4 (*CTLA-4*) mutations[8] and deficiency of adenosine deaminase 2 (*DADA2*).[9] Constitutional syndromes are classically manifested in childhood, often with characteristic physical anomalies; typically, multiple organs are involved. The family history may disclose affected relatives. However, genetic and genomic testing has revealed that genetic deficiencies can appear in adults, who may present without these typical features. Recognition of a germline cause is critical for guiding therapy

Table 1. Constitutional Marrow Failure Syndromes in Adults.*

Syndrome	Hematologic Presentation	Clinical Features	Genetic Features	Pathophysiological Features
Telomere diseases	SAA in childhood; MAA, macrocytic anemia, thrombocytopenia in adulthood	Early hair graying, pulmonary fibrosis, hepatic cirrhosis	*DKC1, TERT, TERC, RTEL1,* other rare mutations	Deficient telomere repair (telomerase enzyme complex), inadequate telomere protection (shelterin proteins)
Fanconi anemia	SAA in childhood; rare presentation as bone marrow failure, MDS, AML in adulthood	Short stature, café-au-lait spots, skeletal and urogenital anomalies	17 FANC genes	Deficient repair of interstrand DNA cross-links
GATA2 deficiency	SAA, MDS, AML	Persistent and unusual infection (e.g., warts)	*GATA2*	Unknown
CTLA4 deficiency	AA with low IgG	Intestinal disease, adenopathy, infection, autoimmunity	*CTLA4*	Immune de-repression

* AA denotes aplastic anemia, AML acute myeloid leukemia, MAA moderate aplastic anemia, MDS myelodysplastic syndrome, and SAA severe aplastic anemia.

and has consequences for family members. Fatal graft rejection has followed inadvertent use of a graft from an affected sibling[10] and persistent marrow failure after transplantation in patients with mutations in the gene encoding the growth factor thrombopoietin.[11] Results of published surveys from specialty clinics are influenced by referral patterns and case definitions. In a study involving 98 children and adults with aplastic anemia, 5% had genetic mutations on screening.[12] Of 173 patients with bone marrow failure of suspected inherited origin, most of whom were under 18 years of age, about 50% had mutations.[13] At the National Institutes of Health, among children and adults referred for protocol treatments, unexpected pathogenic mutations were very unusual in patients with severe aplastic anemia but were much more prevalent in those with moderate bone marrow failure (Rodrigues F: personal communication).

IMMUNE APLASTIC ANEMIA

Almost all sporadic cases of aplastic anemia, especially when severe and acute, appear to be immune-mediated. The strongest, most relevant evidence for an immune mechanism is improvement in blood counts after a variety of immunosuppressive therapies and dependence of adequate counts after recovery on a maintenance calcineurin inhibitor (usually cyclosporine).[14] Aplastic anemia is associated with immunologic diseases (particularly seronegative hepatitis,[15] eosinophilic fasciitis,[16] and thymoma[17]), but most cases do not have a clear cause and have been labeled idiopathic.

Immune aplastic anemia lies on a spectrum of bone marrow and blood-cell diseases (Fig. 2B). Cytotoxic T cells have been the focus in studies of samples from affected patients and in vitro studies. These cells appear to be functionally and phenotypically activated,[18,19] skewed to produce type 1 cytokines (e.g., interferon-γ),[20,21] induce apoptosis through Fas and the Fas ligand,[22] and circulate as oligoclones.[23] Acquired, somatic mutations in the signal transducer and activator of transcription 3 (STAT3) signaling pathway may be pathogenic in some cases of aplastic anemia, as they are in large granular lymphocytosis, producing constitutively activated T cells.[24] Regulatory T (Treg) cells are decreased in patients with aplastic anemia and increase with a hematologic response.[25,26]

Aplastic anemia is associated with specific histocompatibility antigens.[27] The presence of "escape clones" (granulocytes with loss of the region of chromosome 6 that encompasses HLA alleles) in 10 to 15% of patients is striking[28,29]; cells selected because of the absence of HLA, acquired by 6p loss of heterozygosity (LOH) or somatic mutations, sustain hematopoiesis by means of clonal expansion.[30] Immune escape has also been hypothesized to explain clonal expansion of "PNH cells" in aplastic anemia; red cells and white cells deficient in glycosylphosphoinositol (GPI)–anchored proteins originate from a stem cell with an acquired mutation in *PIGA* (phosphatidylinositol glycan class A).[31] It has been

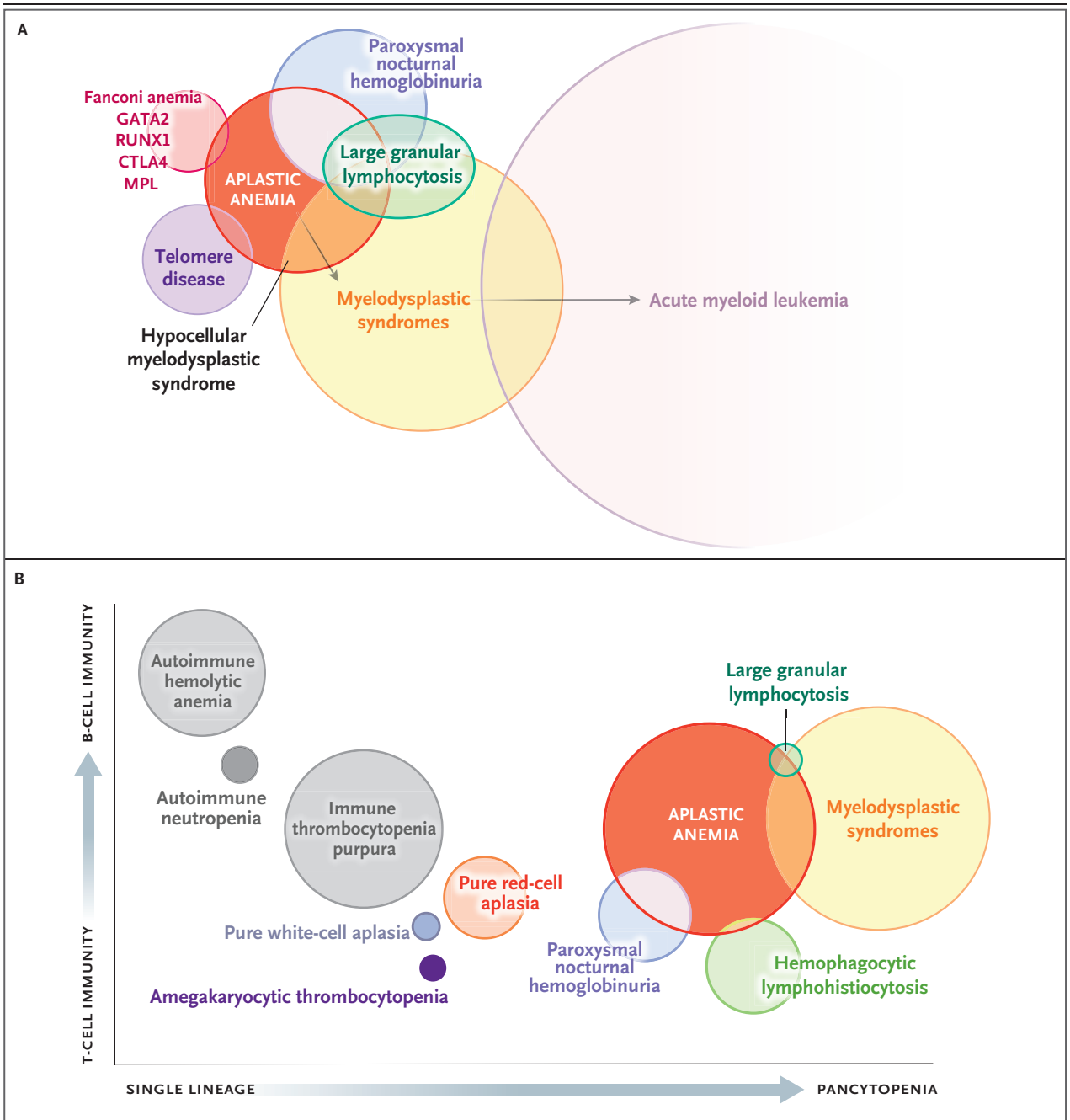

Figure 2. Aplastic Anemia in Relationship to Other Diseases.

The Venn diagram in Panel A highlights the overlap of aplastic anemia, both diagnostically and pathophysiologically, with paroxysmal nocturnal hemoglobinuria, myelodysplastic syndromes, and constitutional marrow failure syndromes. Many clinical and pathophysiological features of aplastic anemia parallel those of other immune-mediated diseases in which a single organ is targeted. Panel B shows the spectrum of immune cytopenias. The dominant immune effectors are delineated on the y axis; for example, autoimmune destruction of peripheral-blood cells is mainly antibody-mediated, whereas T cells have been implicated in marrow destruction. However, the immune response is almost certainly complex in all these diseases. (For schematic purposes, the circles in each Venn diagram have been scaled to the relative numbers of PubMed citations.)

suggested that the GPI anchor itself is a target of the immune response.[32] Autoantibodies of uncertain clinical relevance have been identified by high-throughput screening of serum samples,[33,34] but the inciting antigen (or antigens) for the dominant T-cell response remains unknown.

Immune aplastic anemia can be modeled in mice: infusion of mismatched donor lymphocytes leads to rapid hematopoietic failure and death.[35,36] Limited numbers of T cells specifically attack marrow cells, causing apoptosis through Fas engagement; type 1 cytokines have an active role in targeted cell death, directly for interferon-γ and indirectly for tumor-necrosis factor α (TNF-α); and Treg cells are inhibitory.

HEMATOPOIESIS

STEM-CELL NUMBER

Aplastic anemia has long been regarded as the result of a profound deficit in hematopoietic stem and progenitor cells.[37] The marrow is devoid of morphologic precursors to erythrocytes, granulocytes, and platelets. Cells bearing the antigen CD34, which contain stem and progenitor cells, are almost completely absent in fixed biopsy specimens or on flow-cytometric analysis. Colony-forming cells for differentiated lineages and more immature multipotent cells are extremely low in number. None of the available measurements of hematopoiesis accurately quantify stem cells, and they also do not correlate closely with blood counts. A return to normal blood counts and bone marrow function after immunosuppression, and even more dramatically with growth factor stimulation, indicates the presence of residual stem cells in an "empty" bone marrow.

STEM-CELL CLONALITY

Hematopoiesis in aplastic anemia is clonal, but this is not a well-defined term.[38] Cancer is clonal: a tumor is derived from a single malignant cell. Normal hematopoiesis is also clonal: a single stem cell gives rise to many differentiated progeny. In a tumor or leukemia, mutations in specific genes alter cell function and in combination produce the malignant phenotype. Mutations also accumulate in normal cells as "passengers," in genes that do not lead to gross functional changes. Clonal populations may be easier to detect in patients with marrow failure than in healthy persons with many more active stem cells. Mutated clones need not be malignant. In aplastic anemia, benign clonal populations of granulocytes deficient in GPI-anchored proteins or lacking HLA expression are common, presumably selected for their survival under immune attack. Indeed, healthy persons have tiny numbers of leukocytes with *PIGA* mutations, and chromosomal clonal mosaicism is present in many normal tissues. Clonal evolution in aplastic anemia is development of the myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML), usually characterized by aneuploidy, especially loss of all or a portion of chromosome 7. Abnormalities of chromosome 7 are a feature of both acquired[39] and constitutional[40] aplastic anemia, suggesting that the environment of marrow failure itself confers a predisposition to their selection.

With next-generation sequencing, clonality is detected in leukocytes with a mutation in a specific gene. In most targeted genomic studies, mutations are queried in about 50 "candidate" genes (i.e., genes known to be recurrently mutated in MDS and AML). (These mutations are acquired, not inherited, and are present in a hematopoietic stem cell and its progeny.[41]) Such clonal populations are present in about one third of patients with aplastic anemia, but in contrast to MDS and AML, a very limited set of genes (*DNMT3A*, *ASXL1*, and *BCOR*) is involved, and the clone size (variant allele fraction) is small.[42,43] Mutated clones are associated with prognosis (favorable with *BCOR* and *PIGA* and unfavorable with *DNMT3A* and *ASXL1*).[42] Clones containing mutations in these genes can be stable over a period of many years,[42] and mutated clones infrequently appear to drive evolution to a myeloid cancer.[44,45]

TELOMERES

Extremely short telomeres are a typical finding in patients with a genetic telomere disease. In immune aplastic anemia, telomere length may be decreased as a result of increased mitotic demand on a limited pool of stem cells.[46] Telomere length at diagnosis has correlated with outcomes,[45,47] response to immunosuppression,[48] and evolution

to MDS and AML.[47] Accelerated telomere attrition precedes progression to monosomy 7.[44]

DIAGNOSIS

The fatty bone marrow remains a basic diagnostic feature of aplastic anemia, but sophisticated testing can now be directed at distinguishing among diverse pathophysiological disorders and discriminating among similar, sometimes overlapping diseases in the differential diagnosis (Fig. 2B). Accurate diagnosis is required for appropriate therapy and effective management.

CONSTITUTIONAL VERSUS ACQUIRED BONE MARROW FAILURE

Genomic screening complements functional testing for Fanconi anemia (indicated by chromosomal damage after clastogenic stress) and telomeropathies (indicated by shortened telomeres). However, comprehensive germline screening adds to the cost of the evaluation, and the results may not be available to the clinician for several weeks. Screening for the approximately 50 genes that cause constitutional marrow failure is particularly valuable in moderate and chronic pancytopenia, thrombocytopenia, and macrocytic anemia; in children and adolescents; and in patients in whom immunosuppressive therapy has failed. In patients with severe pancytopenia who do not have a family history, clinical features (Table 1), or evidence of organ involvement beyond the marrow, screening is not likely to be positive. Commercial testing reports "pathogenic" mutations, a determination based on amino acid changes and their location in conserved or functionally critical regions of a gene, and requires continual reannotation of the literature for genotype–phenotype correlations. Some base substitutions are infrequent polymorphisms in certain ethnic populations, and their clinical meaning may be uncertain. Conversely, exome sequencing of candidate genes may not detect critical mutations in regulatory regions.[49,50] Correlation of genomic screening with functional testing is desirable, but some patients with telomeropathy have normal telomere length, short telomeres not below the first percentile can be difficult to interpret, and mosaicism due to reversion of a Fanconi anemia gene can lead to a normal chromosomal study in peripheral blood.

HYPOPLASTIC MYELODYSPLASTIC SYNDROME VERSUS APLASTIC ANEMIA

Acquired mutations are detected on genomic screening of recurrently mutated genes in MDS and AML. Such testing is valuable when MDS is suspected. Hypocellular MDS may be suggested from the appearance of the bone marrow, especially dyspoietic megakaryocytes,[51] and a normal or increased number of CD34 cells is not consistent with aplastic anemia. Flow cytometry enumerates CD34 cells and identifies anomalous phenotypes indicating aberrant differentiation.[52] Genomic testing may be useful, since spliceosome gene mutations and multiple mutated genes are characteristic of MDS but not of aplastic anemia.[53] However, the genomic pattern of hypoplastic MDS — involvement of specific genes, the likelihood of a single gene mutation, and clone size — is both similar to the pattern in aplastic anemia and distinct from that in typical persons and patients with normocellular and hypercellular types of MDS.[54] The finding of a *DNMT3A*- or *ASXL1*-mutated clone does not alter the diagnosis of aplastic anemia or the likelihood of a response to therapy.

PNH AND APLASTIC ANEMIA SYNDROME

Screening for PNH is performed by means of flow cytometry, which precisely measures the proportion of GPI-anchored, protein-deficient erythrocytes and leukocytes. In classic hemolytic PNH, the PNH clone is large, above 50% and sometimes approaching representation of all circulating cells from the mutated clone. A large clone correlates with an increased risk of catastrophic venous clot and is an indication for anticomplement therapy with eculizumab, which corrects intravascular hemolysis and is effective prophylaxis against thrombosis. Clones are generally small in aplastic anemia, requiring monitoring but not treatment. Clinical PNH usually does not develop from tiny clones or in the absence of a clone at diagnosis.[55]

TREATMENTS

Approaches to the treatment of aplastic anemia in children and adults are shown in Figure 3.

BONE MARROW TRANSPLANTATION

Replacement of failed bone marrow is curative of the underlying disease. Historically, transplantation has been limited by its complications

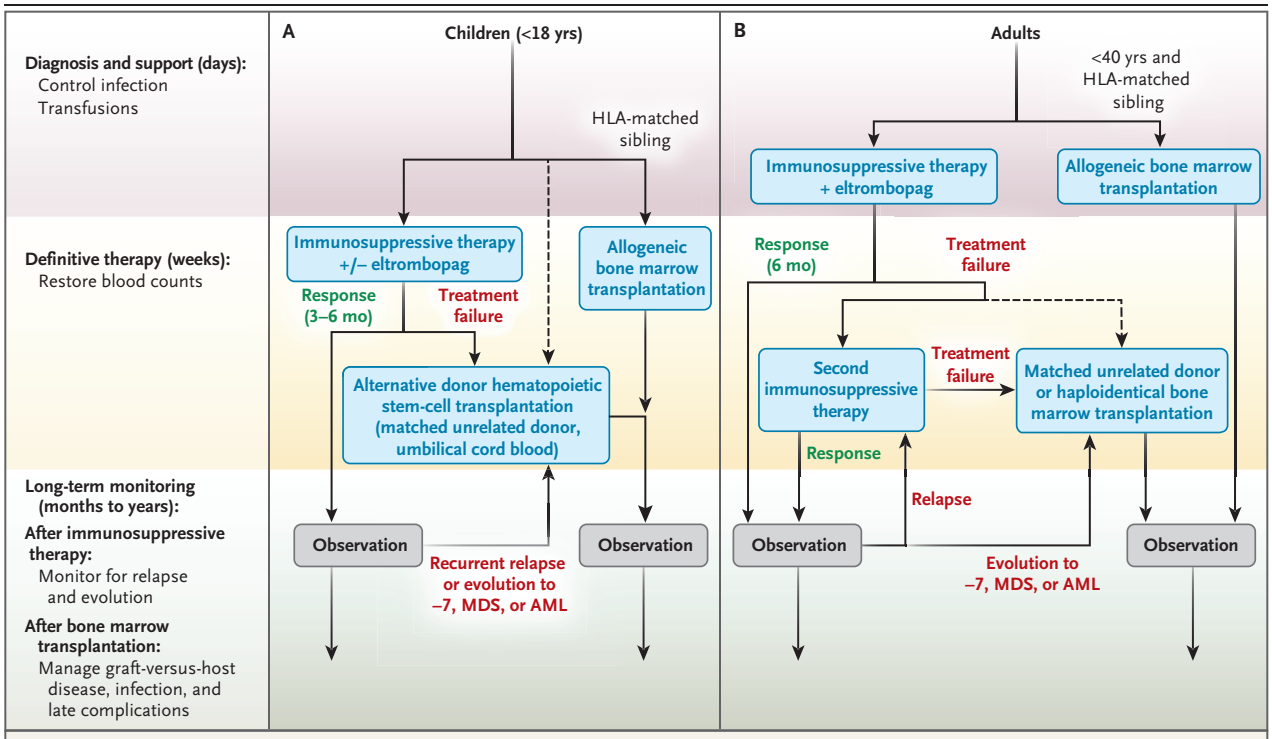

Figure 3. Treatment Algorithms for Patients with Immune Aplastic Anemia.

Treatment algorithms are shown for children (Panel A) and adults (Panel B). The algorithms are intended for guidance. Age thresholds for transplantation are approximate, since clinical decisions in individual patients often depend on multiple factors, such as history, coexisting conditions, and HLA matching. For simplicity, coexisting conditions are not incorporated in the figure, despite their importance. Since hematologists supervise treatment, some secondary and tertiary treatment branches have also been omitted for simplicity. In addition, treatment strategies are not fixed because of developing results. Eltrombopag is likely to be incorporated into first-line treatment and, as a result, will be used less frequently for disease that is refractory to immunosuppressive therapy. Some alternative donor approaches (transplantation from a matched unrelated donor and transplantation of umbilical cord blood) are supported by substantial evidence; other alternative approaches — in particular, transplantation from haploidentical donors — are promising but are based on much less experience, and long-term results have not yet been reported. Shading indicates the stages of treatment: days to diagnose severe pancytopenia and stabilize the patient's condition; weeks to months to select, implement, and complete definitive therapy; and years of monitoring for responses and complications. The ability to manage severe neutropenia[56] is fundamental for good long-term outcomes. Undesirable delays from diagnosis to transplantation should be avoidable when outcomes of immunosuppressive therapy are clear in 3 to 6 months. Patients who do not have a response to immunosuppressive therapy[57-59] or who have complications[60] can do well with second-line transplantation. MDS denotes myelodysplastic syndromes.

— graft rejection and graft-versus-host disease (GVHD) — and the need for suitable donors. Expanded donor options are major recent advances.

For immune aplastic anemia in a young patient, transplantation is always the preferred treatment. When transplantation is undertaken expeditiously after diagnosis, with the use of a graft from a histocompatible sibling donor, the results are excellent, with a long-term survival rate of more than 90% among young children[61,62] and more than 80% among adolescents[63] and a low rate of short- and long-term complications (Table 2). Although transplantation of grafts from sibling donors has become more common in older adults, the results have not improved for several decades, with a survival rate of about 50% for recipients older than 40 years of age[70] and a relative risk of death that is almost three times as high for older adults as it is for children in registry data.[71] Black patients also have poorer outcomes than white patients.[72] Marrow is the preferred source, since the risk of GVHD is higher with the use of peripheral blood.[73,74] Rabbit antithymocyte globulin (ATG) is often added to the conditioning regimen,[64,75] and radiation therapy, especially in children, is avoided.

Histocompatible sibling donors are unavailable for most patients, but large donor registries provide the option of an HLA match with an

Table 2. Hematopoietic Stem-Cell Transplantation for Severe Aplastic Anemia.*

Study	Transplant Source and Recipient Status	No. of Patients	Age	Conditioning and Prophylaxis	Overall Survival	Acute and Chronic GVHD†	Graft Failure
			yr		%	%	%
IBMTR prospective RCT, 1994–2001[64]‡	MFD — 50% of recipients had no previous treatment	70	Median, 23	Conditioning: Cy, ATG Prophylaxis: CsA, MTX	80 at 5 yr	Acute: 11 Chronic: 32	16
King's College retrospective study, 1999–2009[65]§	MFD — most recipients had no previous treatment; MUD — most recipients had refractory disease	100	Median, 18	Conditioning: Alemtuzumab+Cy Prophylaxis: CsA for MSD, FLU+Cy for MUD, FLU+Cy+TBI for mismatched MUD	90 at 5 yr	Acute: 29 Chronic: 3	9
EGBMT registry, children, 2000–2009[61]	MFD — no previous treatment	396	Range, 0–12	Conditioning: mainly Cy, some Cy+FLU Prophylaxis: CsA±ATG±MTX	87 at 3 yr	Acute: 8 Chronic: 6	2
EGBMT registry, adolescents, 2000–2009[63]	MFD — no previous treatment	394	Median, 15	Conditioning: mainly Cy, some Cy+FLU±ATG Prophylaxis: mostly MTX+CsA, some CsA+MMF	86 at 3 yr	Acute: 12 Chronic: 8	8
EGBMT registry, 2005–2009[66]	MFD — previous recipient treatments not described	940	50% >20	—	83 at 5 yr	Acute: 13 Chronic: 6	9
EGBMT registry, 2005–2009[66]	MUD — previous recipient treatments not described	508	53% >20	—	76 at 5 yr	Acute: 26 Chronic: 11	9
French national prospective study, 2011–2015[67]	UCB — refractory SAA	26	Median, 16	Conditioning: FLU+Cy+ATG+TBI Prophylaxis: CsA	85 at 2 yr	Acute: 46 Chronic: 36	12
JSHCT registry, 2001–2012[68]	UCB — refractory adult SAA	69	Median, 49	Conditioning: mainly FLU+melphalan+low-dose TBI Prophylaxis: MTX or MMF± glucocorticoids±CIN	69 at 3 yr	Acute: 32 Chronic: 21	29
Eurocord and EBMT retrospective registry, 1988–2014[69]	Sibling UCB with or without bone marrow — mainly for refractory disease	20	Median, 5.6	Conditioning: variable but mainly Cy+FLU Prophylaxis: variable but mainly CsA+glucocorticoids	81 at 7 yr	Acute: 6 Chronic: 8	10

* ATG denotes antithymocyte globulin, CIN calcineurin inhibitor, CsA cyclosporine, Cy cyclophosphamide, EBMT European Society for Bone Marrow Transplantation, EGBMT European Group for Bone Marrow Transplant, FLU fludarabine, GVHD graft-versus-host disease, IBMTR International Bone Marrow Transplant Registry, JSHCT Japan Society for Hematopoietic Cell Transplantation, MFD matched family donor, MSD matched sibling donor, MTX methotrexate, MUD matched unrelated donor, RCT randomized, controlled trial, TBI total-body irradiation, and UCB umbilical cord blood.

† Data for acute GVHD are for grades II, III, and IV disease. Data for chronic GVHD are usually for grades II, III, and IV (for extensive disease) and occasionally for all chronic GVHD.

‡ This RCT compared Cy alone with Cy plus ATG. There were no significant differences between the conditioning regimens with respect to outcomes. For simplicity, only data for the group that received CTX plus ATG are shown, since this is the more common conditioning regimen.

§ Only data from alemtuzumab-treated patients are shown; MSD and MUD are combined, as they were in the original report.

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unrelated donor at molecular resolution for most white patients.[76-78] In a comprehensive report on more than 500 transplantations, survival after receipt of a transplant from an HLA-matched unrelated donor was not statistically inferior to survival after receipt of a transplant from a matched sibling donor, but the frequency of serious GVHD was twice as high.[77] Young age is a favorable factor for transplantation of grafts from unrelated donors, as it is for transplantation of grafts from sibling donors. For children in whom other therapies have failed, grafts from unrelated donors are associated with excellent survival; the survival rate was 95% in a multicenter British study.[57] Outcomes are better when marrow is transplanted rather than blood cells, ATG is included in the conditioning regimen, donors are young, and the interval between diagnosis and transplantation is short.[77,79] Outcomes have been so good in children that some experts have advocated for first-line use of transplants from unrelated donors,[80,81] despite sometimes protracted delays in identifying and collecting donor cells. Late complications are more frequent in recipients of transplants from unrelated donors than in recipients of transplants from siblings.[82]

Umbilical cord blood transplantation has been successful in aplastic anemia, mainly in children because of the favorable relationship between the cell numbers in the inoculum and the recipient's weight, with survival approximating 90%.[69,83] Rates of GVHD are low. The major disadvantages of cord blood are delayed engraftment and prolonged neutropenia. Some protocols combine cord blood and mismatched bone marrow.[58]

A potential donor who is half-matched to the patient should be present in virtually every family. Since even single antigen disparities markedly affect the outcome of transplantation, overcoming major histocompatibility differences had seemed an insuperable barrier. T-cell–depleting strategies — administration of cytotoxic drugs and biologic agents before transplantation and cyclophosphamide afterward[84] — have been used to prevent GVHD. The results have been encouraging on the basis of extensive experience in Chinese centers, with much smaller series of transplant recipients in the United States and Europe (Table 3). Haploidentical transplantation has been advocated in China as first-line treatment for children.[92] In Europe, with an average 1-year survival rate of about 74%, haploidentical transplantation is recommended as second-line therapy.[93] Current results are promising, but because of the relatively limited numbers of cases reported and the unknown long-term effects of complicated regimens and a mismatched immune system, haploidentical transplantation is regarded as experimental in the United States and Europe.

For the constitutional marrow failure syndromes, transplantation is the only curative option for marrow failure or acute leukemia. Although recipients have the advantage of young age, specific considerations relate to the underlying biology of the syndrome: patients with Fanconi anemia have an inherent sensitivity to alkylating agents in conditioning regimens and an increased risk of late cancers, and patients with telomere disease may have hepatic and pulmonary deterioration after transplantation. Both the decision to perform transplantation and the timing of the procedure can be difficult because of the slow progression of moderate hematopoietic failure, the uncertainty of variable disease outcomes without intervention, and the unpredictable risk of transformation to leukemia. Nevertheless, in some clinical circumstances, improvement has been seen in survival and morbidity over historically poor outcomes.[94-96] For almost 100 patients with constitutional marrow failure who underwent cord-blood stem-cell transplantation, the 7-year survival rate was 86% and most of the patients did not have GVHD.[69] Children with Fanconi anemia who received transplants from unrelated donors had good outcomes, similar to those with transplants from matched family donors.[97] Even among adults with Fanconi anemia who received matched transplants from a sibling after a reduced-intensity conditioning regimen, the survival rate was 85% at 3 years.[98]

IMMUNOSUPPRESSION

In the early years of transplantation, occasional autologous recovery of bone marrow despite graft failure suggested that the antilymphocyte globulin used in conditioning regimens might have had a salutary effect. Combined with cyclosporine, ATG leads to hematologic responses in about two thirds of patients.[14,93] Complex mixtures of antibodies to human proteins that have

Table 3. Haploidentical Hematopoietic Stem-Cell Transplantation for Severe Aplastic Anemia.*

Study	No. of Patients	Median Age	Conditioning and Prophylaxis	Overall Survival	Acute and Chronic GVHD†	Graft Failure
		yr		%	%	*no. of cases*
Prospective study in Korea, 2009–2010[85]	4	18	Conditioning: Cy, FLU, ATG Prophylaxis: CsA, MMF; graft depleted of CD3 or CD3–CD19 cells	100 at 19 mo	0	0
King's College study[86]	6	30	Conditioning: Cy, FLU, low-dose TBI Prophylaxis: Cy (after transplantation), tacrolimus, MMF; GCSF-mobilized peripheral blood	67% at 1 yr	Acute: 17 (skin) Chronic: 0	2 primary
Retrospective study in Brazil, 2010–2014[87]	16	17	Conditioning: Cy, FLU, low-dose TBI Prophylaxis: Cy (after transplantation), CNI, MMF	67% at 1 yr	Acute: 13 Chronic: limited, 20; severe, 7	1 primary, 1 secondary
Multicenter prospective study in China, 2012–2015[88]	101	19	Conditioning: BU, Cy, ATG Prophylaxis: CsA, MMF, MTX	89 at 3 yr	Acute: 34 Chronic: 20 (extensive, 9)	2 secondary
Prospective pediatric study in Beijing, 2007–2015[89]	52	9	Conditioning: BU, Cy, ATG Prophylaxis: CsA, MMF, MTX	85 at 3 yr	Acute: 14 (grade III–IV) Chronic: 13	3 secondary
Multicenter retrospective study in China, 2012–2015[90]	89		Conditioning: BU, Cy, ATG Prophylaxis: CsA, MMF, MTX	86 at 3 yr	Acute: 30 Chronic: 3	1 primary
Johns Hopkins study, 2011–2016[59]	13	30	Conditioning: Cy, FLU, low-dose TBI, ATG Prophylaxis: Cy (after transplantation), MMF, tacrolimus	100 at 21 mo	0	0
Retrospective study in Langfang, China, 2012–2016[91]	41	13	Conditioning: Cy, FLU, BU, ATG, and GCSF-mobilized bone marrow and peripheral blood Prophylaxis: CIN, MMF, MTX	80 at 3 yr	Acute: 44 Chronic: 12	0

* BU denotes busulfan, G-CSF granulocyte colony-stimulating factor, and MMF mycophenolate mofetil.
† Data for acute GVHD are for grade II, III, or IV disease. Patients with chronic GVHD may or may not have had grade II, III, or IV acute GVHD.

not been fully defined, ATGs have a relatively mild lymphocyte-depleting effect, but subtle differences in the mechanism of action appear to be important for efficacy. For example, rabbit ATG was much less efficacious than was horse ATG in a randomized, controlled trial, in which a major difference in biologic effect was more severe depletion of CD4 cells and Treg cells after the administration of rabbit ATG.[26] Even in patients with a response, blood counts do not usually return to normal. Relapse occurs in 30%[99] to 60%[100] of patients and usually responds to further immunosuppression, but years of continued cyclosporine therapy are required.[101] Responses and outcomes are better in children[102] than in older adults.[103] Patients who do not have a response to horse ATG may have improvement with second-line rabbit ATG or alemtuzumab, a pan–T-cell monoclonal antibody.[101,104]

STEM-CELL STIMULATION

Many attempts to improve on ATG by adding androgens, granulocyte colony-stimulating factor, mycophenolate mofetil, or sirolimus have not altered response rates or long-term outcomes.[14] Hematopoietic growth factors are ineffective in aplastic anemia. It was therefore unexpected when eltrombopag, a synthetic mimetic of thrombopoietin, showed activity in patients with refractory aplastic anemia. Approximately half the patients had robust trilineage improvements in blood counts, which in most cases were durable after discontinuation of the drug.[105,106] When eltrombopag was added to initial standard immunosuppressive therapy, it markedly increased the overall response rate to about 80% and the complete response rate to about 50%, with patients often having rapid hematologic recovery.[45] To date, the rates of relapse and evolution to myeloid cancers appear to be similar to or lower than the rates among historical controls treated with immunosuppression alone. Eltrombopag has been approved for use in patients with refractory severe aplastic anemia, and an application has been submitted to the Food and Drug Administration for the use of eltrombopag in combination with immunosuppressive agents as initial therapy for aplastic anemia. In both cases, data came from a single center and limited numbers of patients. RACE (A Prospective Randomized Multicenter Study Comparing Horse Antithymocyte Globuline [hATG] + Cyclosporine A [CsA] with or without Eltrombopag as Front-line Therapy for Severe Aplastic Anemia Patients; ClinicalTrials.gov number, NCT02099747), a multicenter European trial, is testing eltrombopag in combination with ATG in a randomized protocol.

Increases in bone marrow cellularity and the numbers of CD34 and progenitor cells suggest a direct effect of eltrombopag on marrow stem cells.[45] Thrombopoietin concentrations in blood from patients with aplastic anemia are very high,[107] but eltrombopag may evade a block to receptor engagement in the presence of interferon-γ (Alvarado L, Larochelle A: personal communication).

ANDROGENS

Androgens have long been used as therapy for marrow failure syndromes. Although generally regarded as much less efficacious than immunosuppressive strategies for the treatment of severe aplastic anemia, androgens are standard care for many constitutional syndromes. Sex hormones increase expression of the gene for telomerase in cell culture[108] and in mice.[109] In a recent prospective trial, high doses of danazol, a synthetic androgen, improved blood counts in patients with telomere disease and also appeared to reverse accelerated telomere attrition.[110]

CONCLUSIONS

The development of understanding and treatment of aplastic anemia is a success story of the laboratory and clinic, with implications beyond bone marrow failure. The causes of aplastic anemia are related to common environmental toxins, specific viral infections, and genes affecting basic cellular mechanisms. The role of the immune system has been recognized as both potent and subtle. Most gratifying, treatments for patients with immune aplastic anemia have improved remarkably over the past several decades because of the development of better transplantation and immunosuppressive regimens. Transplantation can be beneficial in all types of marrow failure, but in the future, gene editing and restoration of function offer hope for constitutional diseases.

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