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Aplastic anemia

Aplastic anemia: history and recent developments in diagnosis and treatment

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Abstract

Acquired aplastic anemia is an immune-mediated disease that targets hematopoietic stem cells, which is diagnosed by findings of peripheral blood pancytopenia and hypocellular bone marrow. Although the diagnostic definition is simple, differential diagnosis from other overlapping hematopoietic disorders such as hypoplastic myelodysplastic syndrome and inherited bone marrow failure syndrome is not easy. Immune suppressive therapy and allogeneic hematopoietic stem cell transplantation are important treatment approaches for aplastic anemia, and both have advanced in recent years. This issue of Progress in Hematology covers four topics related to aplastic anemia: (1) laboratory markers to identify immune pathophysiology and their role on differential diagnosis and prognosis, (2) the path to combination therapy with horse anti-thymocyte globulin, cyclosporine A, and eltrombopag, (3) more than 60 years of history and recent trends in allogeneic HSCT, and (4) genetic testing for differential diagnosis from IBMFS and novel approaches to transplantation for children including fludarabine/melphalan-based conditioning.

Acquired aplastic anemia is a rare immune disorder targeting hematopoietic stem cells [1]. The incidence of aplastic anemia was reported as 2.34 per million inhabitants per year in a surveillance study in Barcelona [2]. The rate was reported to be slightly higher in Asia, but still low: 3.9 per million-year in a Bangkok survey [3], and 8.3 per million-year in Japanese registry data. Hematologists generally encounter considerably fewer patients with aplastic anemia than patients with acute leukemia. The diagnosis of aplastic anemia is based on findings of peripheral blood pancytopenia and hypocellular bone marrow. The definition of aplastic anemia is simple, but differential diagnosis from other bone marrow failure disorders is challenging. Differentiation from hypocellular myelodysplastic syndrome (MDS) in adults and inherited bone marrow failure syndrome (IBMFS) in children is particularly important in determining the treatment strategy.

Clinical and laboratory findings to date suggest that acquired aplastic anemia is caused by a decrease in hematopoietic stem cells associated with an autoimmune etiology [4, 5]. Shinji Nakao reviewed diagnostic markers such as glycosylphosphatidylinositol-anchored protein-deficient (GPI[−]) blood cells and HLA class I allele-lacking (HLA[−]) leukocytes suggesting immunological attacks on hematopoietic stem cells. Detailed information useful for clinical decision-making is presented, including GPI(−) cell thresholding and its association with chromosomal abnormalities. In parallel with the autoimmune hypothesis, immune suppressive therapy (IST) has been developed, first with anti-thymocyte globulin (ATG) alone [6] and then with ATG + cyclosporine A (CsA) [7]. Phillip Scheinberg provided an overview of the early efforts in IST from about 50 years ago to the recent advancements, including the addition of thrombopoietin receptor agonists (TPO-RAs) [8, 9]. His review illustrates the current treatment paradigm for aplastic anemia.

Around the time the therapeutic effects of ATG were discovered, successful cases of allogeneic bone marrow transplantation (BMT) were reported by Thomas et al. [10], and the era of potentially curative transplantation began. Rainer Storb gave us the history of allogeneic BMT, covering its early challenges up to the first successful case in 1971 and subsequent advances in conditioning and GVHD prophylaxis [11, 12]. As indicated in his review, more recently,

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haploidentical HSCT with post-transplant cyclophosphamide (PTCY) has produced excellent outcomes in patients with treatment-naïve and IST-refractory aplastic anemia [13, 14].

In Japan, umbilical cord blood transplantation (UCBT) has also been explored as an alternative donor transplantation for aplastic anemia [15–17]. However, it had the problem of high second transplantation rates due to graft failure after UCBT [18]. A recent retrospective comparison between haploidentical HSCT with PTCY (PTCY-haplo) and UCBT showed similar survival but higher rates of neutrophil and platelet engraftment in the PTCY-haplo group [19]. It will be important to determine which donor type to prioritize in patients without an HLA-matched donor who are IST-refractory or urgently need transplantation. Nao Yoshida reviewed comprehensive workup including next-generation sequencing for differential diagnosis between acquired aplastic anemia and IBMFS. Advances in transplantation procedures in pediatric patients, including fludarabine/melphalan-based regimens are also discussed [20], and the role of EPAG in children is a point of debate.

In this issue of Progress in Hematology, these reviews by four experts will help physicians to successfully diagnose and treat pediatric and adult patients with aplastic anemia, and will inspire us to make further advances.

Declarations

Conflict of interest Y.O. received honoraria from Pfizer, Novartis, and Kyowa Kirin.

References

1. Young NS, Calado RT, Scheinberg P. Current concepts in the pathophysiology and treatment of aplastic anemia. Blood. 2006;108(8):2509–19. https://doi.org/10.1182/blood-2006-03-010777.
2. Montane E, Ibanez L, Vidal X, Ballarin E, Puig R, Garcia N, et al. Epidemiology of aplastic anemia: a prospective multicenter study. Haematologica. 2008;93(4):518–23. https://doi.org/10.3324/haematol.12020.
3. Issaragrisil S, Chansung K, Kaufman DW, Sirijirachai J, Thamprasit T, Young NS. Aplastic anemia in rural Thailand: its association with grain farming and agricultural pesticide exposure. aplastic anemia study group. Am J Public Health. 1997;87(9):1551–4. https://doi.org/10.2105/ajph.87.9.1551.
4. Sugimori C, Chuhjo T, Feng X, Yamazaki H, Takami A, Teramura M, et al. Minor population of CD55-CD59-blood cells predicts response to immunosuppressive therapy and prognosis in patients with aplastic anemia. Blood. 2006;107(4):1308–14. https://doi.org/10.1182/blood-2005-06-2485.
5. Katagiri T, Sato-Otsubo A, Kashiwase K, Morishima S, Sato Y, Mori Y, et al. Frequent loss of HLA alleles associated with copy number-neutral 6pLOH in acquired aplastic anemia. Blood. 2011;118(25):6601–9. https://doi.org/10.1182/blood-2011-07-365189.
6. Champlin R, Ho W, Gale RP. Antithymocyte globulin treatment in patients with aplastic anemia: a prospective randomized trial. N Engl J Med. 1983;308(3):113–8. https://doi.org/10.1056/NEJM198301203080301.
7. Frickhofen N, Kaltwasser JP, Schrezenmeier H, Raghavachar A, Vogt HG, Herrmann F, et al. Treatment of aplastic anemia with antilymphocyte globulin and methylprednisolone with or without cyclosporine. The german aplastic anemia study group. New Engl J Med. 1991;324(19):1297–304. https://doi.org/10.1056/NEJM199105093241901.
8. Patel BA, Groarke EM, Lotter J, Shalhoub R, Gutierrez-Rodrigues F, Rios O, et al. Long-term outcomes in patients with severe aplastic anemia treated with immunosuppression and eltrombopag: a phase 2 study. Blood. 2022;139(1):34–43. https://doi.org/10.1182/blood.2021012130.
9. Peffault de Latour R, Kulasekararaj A, Iacobelli S, Terwel SR, Cook R, Griffin M, et al. Eltrombopag added to immunosuppression in severe aplastic anemia. New Engl J Med. 2022;386(1):11–23. https://doi.org/10.1056/NEJMoa2109965.
10. Thomas ED, Storb R, Fefer A, Slichter SJ, Bryant JI, Buckner CD, et al. Aplastic anaemia treated by marrow transplantation. Lancet. 1972;1(7745):284–9. https://doi.org/10.1016/s0140-6736(72)90292-9.
11. Storb R, Deeg HJ, Whitehead J, Appelbaum F, Beatty P, Bensinger W, et al. Methotrexate and cyclosporine compared with cyclosporine alone for prophylaxis of acute graft versus host disease after marrow transplantation for leukemia. N Engl J Med. 1986;314(12):729–35. https://doi.org/10.1056/NEJM198603203141201.
12. Storb R, Etzioni R, Anasetti C, Appelbaum FR, Buckner CD, Bensinger W, et al. Cyclophosphamide combined with antithymocyte globulin in preparation for allogeneic marrow transplants in patients with aplastic anemia. Blood. 1994;84(3):941–9.
13. DeZern AE, Zahurak ML, Symons HJ, Cooke KR, Rosner GL, Gladstone DE, et al. Haploidentical BMT for severe aplastic anemia with intensive GVHD prophylaxis including posttransplant cyclophosphamide. Blood Adv. 2020;4(8):1770–9. https://doi.org/10.1182/bloodadvances.2020001729.
14. DeZern A, Zahurak ML, Symons HJ, Cooke KR, Huff CA, Jain T, et al. Alternative donor BMT with post-transplant cyclophosphamide as initial therapy for acquired severe aplastic anemia. Blood. 2023. https://doi.org/10.1182/blood.2023020435.
15. Yamamoto H, Kato D, Uchida N, Ishiwata K, Araoka H, Takagi S, et al. Successful sustained engraftment after reduced-intensity umbilical cord blood transplantation for adult patients with severe aplastic anemia. Blood. 2011;117(11):3240–2. https://doi.org/10.1182/blood-2010-08-295832.
16. Ochi T, Onishi Y, Nasu K, Onodera K, Kobayashi M, Ichikawa S, et al. Umbilical cord blood transplantation using reduced-intensity conditioning without antithymocyte globulin in adult patients with severe aplastic anemia. Biol Blood Marrow Transplant. 2019;25(2):e55–9. https://doi.org/10.1016/j.bbmt.2018.09.039.
17. Hiramoto N, Yamazaki H, Nakamura Y, Uchida N, Murata M, Kondo T, et al. Total body irradiation-containing conditioning regimens without antithymocyte globulin in adults with aplastic anemia undergoing umbilical cord blood transplantation. Ann Hematol. 2022;101(1):165–75. https://doi.org/10.1007/s00277-021-04664-z.
18. Onishi Y, Mori T, Kako S, Koh H, Uchida N, Kondo T, et al. Outcome of second transplantation using umbilical cord blood for graft failure after allogeneic hematopoietic stem cell transplantation for aplastic anemia. Biol Blood Marrow Transplant. 2017;23(12):2137–42. https://doi.org/10.1016/j.bbmt.2017.08.020.

19. Onishi Y, Mori T, Yamazaki H, Hiramoto N, Zaimoku Y, Kanaya M, et al. Comparison of haploidentical stem cell transplantation with post-transplantation cyclophosphamide versus umbilical cord blood transplantation in adult patients with aplastic anemia. Transplant Cell Ther. 2023;29(12):766 e1 e8. https://doi.org/10.1016/j.jtct.2023.09.009.
20. Yoshida N, Takahashi Y, Yabe H, Kobayashi R, Watanabe K, Kudo K, et al. Conditioning regimen for allogeneic bone marrow transplantation in children with acquired bone marrow failure: fludarabine/melphalan vs. fludarabine/cyclophosphamide. Bone Marrow Transplant. 2020;55(7):1272–81. https://doi.org/10.1038/s41409-020-0948-8.