Blood Substitutes

Sara Grethlein, MD, Associate Dean for Graduate Medical Education, Associate Professor, Department of Internal Medicine, Division of Hematology and Oncology, State University of New York at Upstate
Arun Rajan, MD, Fellow in Hematology/Oncology, Division of Hematology/Oncology, Department of Medicine, State University of New York Upstate Medical Center; **Raquel R Bartz, MD,** Staff Physician, Department of Pulmonary/Critical Care Medicine, Duke University Medical Center; **Robert Przybelski, MD,** Assistant Professor, Department of Internal Medicine, University of Wisconsin School of Medicine; **Douglas Coursin, MD,** Director of Anesthesiology/Critical Care Fellowship Training Program, Associate Director of the Trauma and Life Support Center, Professor, Departments of Anesthesiology and Internal Medicine, University of Wisconsin School of Medicine; **Eliot C Williams, MD, PhD,** Professor, Department of Hematology, University of Wisconsin School of Medicine

Updated: Nov 6, 2007

Introduction

The attempt to develop a viable blood substitute spans more than 7 decades. These efforts have essentially focused on the ability of red blood cells to carry oxygen. Hence, most of the products that are in advanced-phase clinical trials are derivatives of hemoglobin and are known as hemoglobin-based oxygen carriers (HBOCs).

Today, an increase in the number of elective surgeries and the still prevalent but small risk of transmission of blood-borne pathogens such as HIV have served as a stimulus to develop a synthetic substitute for human blood, more specifically for development of a red blood cell substitute.

However, to date, no oxygen-carrying blood substitutes are approved for use by the US Food and Drug Administration. This fact highlights not only the challenges that exist in formulating an effective blood substitute but also the immense potential that exists in this field.

The physiology of oxygen transport can be described as follows:

One gram of adult hemoglobin binds to 1.39 milliliters of oxygen. The oxyhemoglobin dissociation curve has a characteristic sigmoid shape due to the cooperative effect that exists between the multiple oxygen binding sites on the hemoglobin molecule. Factors that modify the ability of hemoglobin to bind oxygen include body temperature, pH of blood and the concentration of 2,3-diphosphoglycerate (2,3-DPG).

Characteristics of an Ideal Blood Substitute

The most important adverse effects of blood transfusion relate to the antigenicity of donor blood and its ability to transmit infections. Hence, an ideal blood substitute should lack antigenicity and eliminate, or at least substantially reduce, the ability to transmit infections. In addition, it should be readily available, should have a long half-life, and should be capable of being stored at room temperature. The biologic properties of an ideal blood substitute should include a reasonable amount of oxygen delivery, when compared to normal human red blood cells.[1]

Potential Uses

If such a blood substitute were indeed developed, it would presumably play a major role in the setting of trauma care and for elective surgeries. It would also benefit patients with medical conditions who are in need of long-term blood transfusions, such as patients with myelodysplastic syndrome and aplastic anemia. These products could also be used as organ preservatives to prevent or decrease reperfusion injury to donor organs. Religious and ethnic groups with concerns regarding the use of human derived blood products may accept these substances, which would provide a significant patient care advance.

First-Generation Products

Perfluorocarbon emulsions

Perfluorocarbons are chemically inert molecules containing primarily, as the name suggests, fluorine and carbon atoms. They are capable of dissolving large amounts of many gases, including oxygen. These molecules are hydrophobic in nature, and hence have to be emulsified prior to intravenous administration.[2]

After intravenous administration, the droplets of this emulsion are taken up by the reticuloendothelial system and then slowly broken down. They are then transported to blood, where they are bound to lipids and move to the lungs. In the absence of significant in vivo metabolism, perfluorocarbons are removed from the body by exhalation.

Perfluorocarbons demonstrate a linear oxygen dissociation curve in contrast to the sigmoid dissociation curve of blood. Hence, elevated arterial partial pressures of oxygen enhance oxygen transport by these molecules. However, this linear relationship can also work as a disadvantage since most of the oxygen is released prior to the arrival of the oxygen-laden molecule in the capillary network where the partial pressure of oxygen is lower, and hence the need for oxygen is greater.

Among the various perfluorocarbon emulsions that have been developed are the molecules perfluorooctyl bromide (perflubron), perfluorodecyl bromide, and perfluorodichlorooctane.

The first product to be marketed contained perfluorodecalin and perfluorotripropylamine emulsified with Pluronic F-68 and called Fluosol-DA. It was manufactured by the Green Cross Corporation (Japan) and Alpha Therapeutics (Grifols USA, Los Angeles, Calif). It was approved by the FDA for use in percutaneous transluminal coronary angioplasty. However, due to marginal efficacy, a short effective half-life, temperature instability, low oxygen-carrying capacity, and adverse effects such as acute complement activation and disruption of pulmonary surfactant, this product has since been withdrawn from the market.

A more stable emulsion containing 58% weight per volume perfluorooctyl bromide and 2% weight per volume perfluorodecyl bromide emulsified in 3.6% weight per volume egg yolk phospholipid concentrated to 60% weight per volume was then developed by Alliance Pharmaceutical Corporation (San Diego, Calif). With greater stability at room temperature than Fluosol-DA and with an increased oxygen carrying capacity (4-5 times greater than Fluosol-DA) this compound, called Oxygent, showed great promise initially. However recent phase III trials have shown an increased incidence of stroke in treated patients compared to controls and trials have been halted.[3]

Other PFC emulsions that have been developed include Perftoran (Synthetic Blood International, Costa Mesa, Calif; also developed and in use in Russia), Oxycyte (Synthetic Blood International, Costa Mesa, Calif; entering phase II trials), and Oxyfluor (HemaGen/perfluorocarbon, St Louis, Mo; discontinued due to safety issues).[4]

Stroma-Free Hemoglobin

Stroma-free hemoglobin has been investigated as an oxygen carrier since the 1940s, when researchers realized that native hemoglobin is not antigenic. A solution containing stroma-free hemoglobin has many advantages over red blood cells, including the ability to withstand sterilization and a shelf life of approximately 2 years at room temperature for some products.

Solutions of acellular hemoglobin are not as effective at oxygenation as packed red blood cells because of their high affinity for oxygen. Red blood cells have adapted to release oxygen at an oxygen half saturation pressure of hemoglobin (p-50) of approximately 26.5 mm Hg. This is due to the allosteric effect of 2,3-bisphosphoglycerate (2,3-BPG), which shifts the oxyhemoglobin dissociation curve to the right. In the absence of 2,3-BPG, stroma-free hemoglobin has a p-50 of 12-14 mm Hg.

Unmodified free hemoglobin, when infused rapidly, splits into dimers and is cleared by glomerular filtration and uptake by the reticuloendothelial system.

When free hemoglobin was used initially, it caused a substantial increase in oncotic pressure because of its hyperosmolarity. Unfortunately, the initial attempts at transfusing stroma-free hemoglobin produced renal dysfunction, coagulopathy, and hypertension. Adverse effects were attenuated by various modifications to the hemoglobin molecule to prevent glomerular filtration and to stabilize the molecule to withstand heat and chemical purification during production. Hypertension induced by infusion of these products was out of proportion to the volume infused and has been more difficult to prevent. It is thought to result from hemoglobin binding to nitric oxide, which is a potent vascular endothelial relaxant.

Several approaches have been tried to decrease the avidity with which hemoglobin binds to oxygen. These adaptations include the addition of organic phosphate to serve the function of 2,3-BPG and adenosine triphosphate, cross-linking dimers of hemoglobin tetramers and polymerizing the tetramers to decrease oncotic pressure and prevent glomerular filtration. Hypertension has remained a significant adverse effect of stroma-free hemoglobin.

Diaspirin cross-linked hemoglobin (DCLHb) is the prototype molecule of this category of blood substitutes. It consists of cross-linking between the two alpha chains that lend stability to the molecule. The cross-linking agent is bis (dibromosalicyl) fumarate (DBBF). DCLHb made from outdated human blood has a shelf life of approximately 9 months when frozen and 24 hours when refrigerated. The intravascular half-life is 2-12 hours and is dose dependant. Clinical trials proved that this compound did indeed raise blood oxygen content. However, it also caused intense vasoconstriction resulting in increased systemic pressure, reduced cardiac output, and increased vascular resistance. Hence, no net benefit was derived from this product.

A great deal of work on DCLHb was initially performed by the US Army. They contracted Baxter Healthcare (Deerfield, Ill) to produce DCLHb (HemAssist) on a large scale. However, due to significant adverse effects associated with it, the army discontinued further development of this molecule. Subsequently, Baxter Healthcare halted further development of DCLHb in 1998 after the product failed trials in patients with stroke and trauma.[4]

The first recombinant hemoglobin product, rHb 1.1 (Optro, Somatogen and Eli Lilly) was a genetically engineered variant of human hemoglobin, Hemoglobin Presbyterian, with

modifications to decrease its oxygen affinity. The product was produced in *Escherichia coli* and had an intravascular half-life of 2-19 hours and a shelf life of 18 months when refrigerated. The adverse effect profile was similar to DCLHb and consisted of vasoconstriction, GI distress, fever, chills, and backache. Currently, the production of this compound has been discontinued due to significant adverse effects. Similarly, rHb 2.0, a recombinant hemoglobin produced by Baxter Healthcare had an adverse safety profile that resulted in discontinuation of production.

The development of polymerized hemoglobin was also a result of significant adverse effects caused by intravenous infusion of stroma-free hemoglobin. The cross-linking agent in this case was glutaraldehyde. However, it was discovered that the Hb-glutaraldehyde polymerization reaction was difficult to control and resulted in the formation of products of various molecular sizes.

PolyHeme (Northfield Laboratories Inc., Evanston, Ill) is a first-generation pyridoxylated polymerized hemoglobin made from outdated human blood. It is one of the few products currently being evaluated in a phase III clinical trial that is enrolling patients. It has a half-life of 24 hours, a shelf life longer than 12 months when refrigerated, and a p-50 of 28-30 mm Hg. In a phase II trial in 44 patients with acute trauma, PolyHeme reduced the required the number of allogenic red blood cell transfusions. Results of a trial published in 2002 showed that 75% of patients with red cell hemoglobin levels less than 1 gm% survived traumatic injury after receiving PolyHeme as compared to 16% of historical controls at the same hemoglobin level.[5]

Northfield laboratories is currently involved in a 720-patient phase III trial in trauma patients in which subjects are randomized to receive either PolyHeme or standard of care at the time of injury. On reaching the hospital, patients in the control arm receive blood as indicated whereas patient in the PolyHeme arm continue to receive PolyHeme for 12 hours, and then receive blood, as indicated. Preliminary results have indicated that 46 of 349 patients treated with PolyHeme died whereas 35 out of 363 patients in the control group died. The difference in mortality between the 2 groups at 30 days was not significant. Therefore, the trial seemed to show that although PolyHeme was not inferior to standard of care, it was not superior to it either. The results of this trial are expected to be available sometime in 2007.

Other first-generation polymerized hemoglobin products include HbOC-201 (Hemopure manufactured by Biopure Corporation, Cambridge, Mass) and HemoLink (Hemosol Corporation, Mississauga, Canada).

Hemopure is a polymerized form of bovine hemoglobin with a p-50 of 30 mm Hg that is closer to human hemoglobin than stroma-free hemoglobin. It has an intravascular half-life of 8-23 hours and a shelf life of 36 months at room temperature. Hemopure is approved in South Africa for the treatment of adult surgical patients who are acutely anemic with the intention of eliminating or reducing the need for allogenic red blood cell transfusions. In the United States, phase II trials have been put on hold due to safety issues. In December 2006, the Blood Products Advisory Committee of the FDA voted against recommending that the US Navy proceed with late-phase clinical trials of Hemopure. The main reason for this was the adverse effect profile of this compound since previous studies had shown that Hemopure could increase the risk of strokes and myocardial infarction. Biopure is currently addressing the FDA's questions regarding safety and efficacy of the product.

Next-Generation Blood Substitutes

Polyethylene glycol (PEG) hemoglobin (Enzon Pharmaceuticals, Bridgewater, NJ) was a conjugated bovine hemoglobin that was evaluated for use in cancer therapy to increase tumor oxygenation and enhance the efficacy of radiation and chemotherapy. However, at present, production of this product has been discontinued.

Hemospan (Sangart Inc., San Diego, Calif) is a PEG-conjugated human hemoglobin currently undergoing clinical trials in the US and Europe.[6] In animal models Hemospan has been shown to be effective in cases of hemorrhagic shock.[7] Adverse effects associated with the vasoactive properties of first-generation blood substitutes are not seen with Hemospan. At relatively low concentrations, Hemospan is capable of transporting large amounts of oxygen. Sangart Inc. announced positive results from a phase II study for this product in November 2005.

The trial, conducted in Sweden, involved 90 patients undergoing hip arthroplasty. Patients were randomized to receive either Hemospan or Ringer acetate (control) prior to induction of spinal anesthesia. Hemospan was found to be well tolerated in the study group with no serious adverse effects attributed to the product during the trial period. The percentage of hypotensive episodes in the Hemospan group was about 45% compared to 87% among controls. Incidence of intra-operative vasopressor use was about 15% in the Hemospan group compared to 32% among controls. See Sangart Press for more information.

Pyridoxylated hemoglobin polyoxyethylene conjugate (PHP) is a conjugated hemoglobin developed by Apex Bioscience that is currently undergoing a phase III trial in patients with shock associated with systemic inflammatory response syndrome. The study has been designed to evaluate the safety and efficacy of continuous IV infusion of PHP plus conventional vasopressor treatment versus continuous IV infusion of Plasma-lyte A plus conventional vasopressors as a treatment for restoring hemodynamic stability in SIRS patients with shock. See ClinicalTrials.gov, Identifier: NCT00021502, for more information.

For hemoglobin-based oxygen carriers cross-linked with enzymes, there has been an effort to synthesize compounds that not only perform the function of carrying oxygen, as do the molecules mentioned previously, but also harbor some of the enzyme activity that normal red blood cells possess. Polymerized hemoglobin has been cross-linked with catalase and superoxide dismutase to form a compound that, in animal models can not only carry oxygen but also remove oxygen radicals that are responsible for ischemia reperfusion injuries.[8]

Polyhemoglobin has also been cross-linked with tyrosinase to form a soluble complex that can carry oxygen and decrease the systemic levels of tyrosine. This agent can help increase the efficacy of chemotherapy and radiation therapy in tumor tissue and in a melanoma model has been shown to delay tumor growth without having significant adverse effects.[8]

Efforts have been made to encapsulate hemoglobin within a lipid-membrane to create a compound capable of carrying oxygen while not being associated with significant vasoconstriction. These liposomes appear to be retained in plasma for a significant period. However, they are difficult to produce and can activate the reticuloendothelial system, the complement pathway, and platelets. At present, the only institutions working actively on this product are in Japan.

The ultimate RBC substitute would contain not only hemoglobin but also other contents of the red blood cell also encapsulated in an artificial membrane. However, production of such

a product would be extremely challenging. Efforts have been made to use polyactide, a biodegradable polymer that is converted to lactic acid in the body, to create artificial red blood cells. These cells contain hemoglobin along with the RBC enzyme complement including superoxide dismutase, methemoglobin reductase, and catalase.[8]

Adverse Effects Related to Blood Substitutes

Adverse effects associated with hemoglobin-based oxygen carriers include hypertension, abdominal pain, skin rash, diarrhea, jaundice, hemoglobinuria, oliguria, fever, stroke, and laboratory anomalies such as an elevation in lipase levels. Although most of these side effects were transient and clinically asymptomatic, many clinical trials involving these agents have been discontinued or held due to the associated adverse effects.

Conclusions

Despite many years of research, the ideal blood substitute continues to elude researchers. Most of the initial attempts at synthesizing blood substitutes failed because of significant adverse effects. However, continued research has helped us better understand the physiology of red blood cells and the interactions of RBCs with their surrounding environment. This has helped in developing newer products that do not have significant vasoactive properties, as did the first-generation compounds.

Hopefully, as better blood substitutes are developed and enter routine clinical use, the need for blood transfusions in the operative and trauma settings will decrease. Large-scale production of blood substitutes would also help to meet the anticipated increase in demand for blood as the population ages and the blood donor pool diminishes.

References

1. Moore EE, Johnson JL, Cheng AM, Masuno T, Banerjee A. Insights from studies of blood substitutes in trauma. *Shock*. Sep 2005;24(3):197-205. [Medline].

2. Spahn DR. Blood substitutes. Artificial oxygen carriers: perfluorocarbon emulsions. *Crit Care*. 1999;3(5):R93-7. [Medline].

3. Keipert P. Oxygent, a perfluorochemical-based oxygen therapeutic for surgical patients. In: Winslow R, ed. *Blood Substitutes*. London: Elsevier Inc; 2006:312-323.

4. Winslow RM. Current status of oxygen carriers ('blood substitutes'): 2006. *Vox Sang*. Aug 2006;91(2):102-10. [Medline].

5. Carson JL, Noveck H, Berlin JA, Gould SA. Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. *Transfusion*. Jul 2002;42(7):812-8. [Medline].

6. Vandegriff KD, Malavalli A, Wooldridge J, Lohman J, Winslow RM. MP4, a new nonvasoactive PEG-Hb conjugate. *Transfusion*. Apr 2003;43(4):509-16. [Medline].

7. Young MA, Riddez L, Kjellström BT, Bursell J, Winslow F, Lohman J. MalPEG-hemoglobin (MP4) improves hemodynamics, acid-base status, and survival after uncontrolled hemorrhage in anesthetized swine. *Crit Care Med*. Aug 2005;33(8):1794-804. [Medline].

8. Chang TM. Blood substitutes based on nanobiotechnology. *Trends Biotechnol*. Aug 2006;24(8):372-7. [Medline].

9. Cohn SM. Blood substitutes in surgery. *Surgery*. Jun 2000;127(6):599-602. [Medline].

10. Cohn SM. Is blood obsolete?. *J Trauma*. Apr 1997;42(4):730-2. [Medline].

11. Creteur J, Sibbald W, Vincent JL. Hemoglobin solutions--not just red blood cell substitutes. *Crit Care Med*. Aug 2000;28(8):3025-34. [Medline].

12. Frietsch T, Lenz C, Waschke KF. Artificial oxygen carriers. *Eur J Anaesthesiol*. Sep 1998;15(5):571-84. [Medline].

13. Goodnough LT, Scott MG, Monk TG. Oxygen carriers as blood substitutes. Past, present, and future. *Clin Orthop*. Dec 1998;(357):89-100. [Medline].

14. Gould SA, Moore EE, Hoyt DB, et al. The first randomized trial of human polymerized hemoglobin as a blood substitute in acute trauma and emergent surgery. *J Am Coll Surg*. Aug 1998;187(2):113-20; discussion 120-2. [Medline].

15. Gulati A, Barve A, Sen AP. Pharmacology of hemoglobin therapeutics. *J Lab Clin Med*. Feb 1999;133(2):112-9. [Medline].

16. Henry S, Scalea TM. Resuscitation in the new millennium. *Surg Clin North Am*. Dec 1999;79(6):1259-67, viii. [Medline].

17. Hess JR. Blood substitutes. *Semin Hematol*. Oct 1996;33(4):369-78. [Medline].

18. Hughes GS Jr, Antal EJ, Locker PK. Physiology and pharmacokinetics of a novel hemoglobin-based oxygen carrier in humans. *Crit Care Med*. May 1996;24(5):756-64. [Medline].

19. Ketcham EM, Cairns CB. Hemoglobin-based oxygen carriers: development and clinical potential. *Ann Emerg Med*. Mar 1999;33(3):326-37. [Medline].

20. LaMuraglia GM, O'Hara PJ, Baker WH. The reduction of the allogenic transfusion requirement in aortic surgery with a hemoglobin-based solution. *J Vasc Surg*. Feb 2000;31(2):299-308. [Medline].

21. Lamy ML, Daily EK, Brichant JF. Randomized trial of diaspirin cross-linked hemoglobin solution as an alternative to blood transfusion after cardiac surgery. The DCLHb Cardiac Surgery Trial Collaborative Group. *Anesthesiology*. Mar 2000;92(3):646-56. [Medline].

22. Mullon J, Giacoppe G, Clagett C, et al. Transfusions of polymerized bovine hemoglobin in a patient with severe autoimmune hemolytic anemia. *N Engl J Med*. Jun 1 2000;342(22):1638-43. [Medline].

23. Patel MJ, Webb EJ, Shelbourn TE. Absence of immunogenicity of diaspirin cross-linked hemoglobin in humans. *Blood*. Jan 15 1998;91(2):710-6. [Medline].

24. Przybelski RJ, Daily EK, Kisicki JC. Phase I study of the safety and pharmacologic effects of diaspirin cross-linked hemoglobin solution. *Crit Care Med*. Dec 1996;24(12):1993-2000. [Medline].

25. Rabinovici R, Rudolph AS, Vernick J, et al. A new salutary resuscitative fluid: liposome encapsulated hemoglobin/hypertonic saline solution. *J Trauma*. Jul 1993;35(1):121-6; discussion 126-7. [Medline].

26. Saxena R, Wijnhoud AD, Carton H. Controlled safety study of a hemoglobin-based oxygen carrier, DCLHb, in acute ischemic stroke. *Stroke*. May 1999;30(5):993-6. [Medline].

27. Scott MG, Kucik DF, Goodnough LT. Blood substitutes: evolution and future applications. *Clin Chem*. Sep 1997;43(9):1724-31. [Medline].

28. Sloan EP, Koenigsberg M, Gens D. Diaspirin cross-linked hemoglobin (DCLHb) in the treatment of severe traumatic hemorrhagic shock: a randomized controlled efficacy trial. *JAMA*. Nov 17 1999;282(19):1857-64. [Medline].

29. Spahn DR, van Brempt R, Theilmeier G, et al. Perflubron emulsion delays blood transfusions in orthopedic surgery. European Perflubron Emulsion Study Group. *Anesthesiology*. Nov 1999;91(5):1195-208. [Medline].

30. Viele MK, Weiskopf RB, Fisher D. Recombinant human hemoglobin does not affect renal function in humans: analysis of safety and pharmacokinetics. *Anesthesiology*. Apr 1997;86(4):848-58. [Medline].

Keywords

oxygen carriers, artificial oxygen carriers, oxygen-carrying volume expanders, oxygen-carrying blood substitutes, hemoglobin-based oxygen carriers, perfluorocarbons, blood substitutes, stroma-free hemoglobin, hemoglobin-based oxygen carriers, HBOC

Contributor Information and Disclosures

Author

Sara Grethlein, MD, Associate Dean for Graduate Medical Education, Associate Professor, Department of Internal Medicine, Division of Hematology and Oncology, State University of New York at Upstate
Sara Grethlein, MD is a member of the following medical societies: American Society of Hematology
Disclosure: Nothing to disclose

Coauthor(s)

Arun Rajan, MD, Fellow in Hematology/Oncology, Division of Hematology/Oncology, Department of Medicine, State University of New York Upstate Medical Center
Disclosure: Nothing to disclose

Raquel R Bartz, MD, Staff Physician, Department of Pulmonary/Critical Care Medicine, Duke University Medical Center
Raquel R Bartz, MD is a member of the following medical societies: American Thoracic

Society
Disclosure: Nothing to disclose

Robert Przybelski, MD, Assistant Professor, Department of Internal Medicine, University of Wisconsin School of Medicine
Robert Przybelski, MD is a member of the following medical societies: American Academy of Family Physicians
Disclosure: Nothing to disclose

Douglas Coursin, MD, Director of Anesthesiology/Critical Care Fellowship Training Program, Associate Director of the Trauma and Life Support Center, Professor, Departments of Anesthesiology and Internal Medicine, University of Wisconsin School of Medicine
Douglas Coursin, MD is a member of the following medical societies: American College of Chest Physicians, American Society of Anesthesiologists, and Society of Critical Care Medicine
Disclosure: Nothing to disclose

Eliot C Williams, MD, PhD, Professor, Department of Hematology, University of Wisconsin School of Medicine
Eliot C Williams, MD, PhD is a member of the following medical societies: American Society of Hematology
Disclosure: Nothing to disclose

Medical Editor

S Gerald Sandler, MD, FACP, FCAP, Professor of Medicine and Pathology; Director, Transfusion Medicine, Department of Laboratory Medicine, Georgetown University Hospital
S Gerald Sandler, MD, FACP, FCAP is a member of the following medical societies: American Association of Blood Banks, American College of Physicians, American Society of Hematology, College of American Pathologists, and International Society of Blood Transfusions
Disclosure: Nothing to disclose

Pharmacy Editor

Francisco Talavera, PharmD, PhD, Senior Pharmacy Editor, eMedicine
Disclosure: Nothing to disclose

Managing Editor

Marcel E Conrad, MD, BS, (Retired) Distinguished Professor of Medicine, University of South Alabama
Marcel E Conrad, MD, BS is a member of the following medical societies: Alpha Omega Alpha, American Association for the Advancement of Science, American Association of Blood Banks, American Chemical Society, American College of Physicians, American Physiological Society, American Society for Clinical Investigation, American Society of Clinical Oncology, American Society of Hematology, Association of American Physicians, Association of Military Surgeons of the US, International Society of Hematology, Society for Experimental Biology and Medicine, and Southwestern Oncology Group
Disclosure: Nothing to disclose

CME Editor

Rajalaxmi McKenna, MD, FACP, Consulting Staff, Department of Medicine, Southwest Medical Consultants, SC, Good Samaritan Hospital, Advocate Health Systems
Rajalaxmi McKenna, MD, FACP is a member of the following medical societies: American Society of Clinical Oncology, American Society of Hematology, and International Society on Thrombosis and Haemostasis
Disclosure: Nothing to disclose

Chief Editor

Emmanuel C Besa, MD, Professor, Department of Medicine, Division of Hematologic Malignancies, Kimmel Cancer Center, Thomas Jefferson University
Emmanuel C Besa, MD is a member of the following medical societies: American Association for Cancer Education, American College of Clinical Pharmacology, American Federation for Medical Research, American Society of Clinical Oncology, American Society of Hematology, and New York Academy of Sciences
Disclosure: Nothing to disclose