Practical Clinical Consensus Guidelines for the Management of Cancer Associated Anemia in Low- and Middle-Income Countries

Purvish Mahendra Parikh[1] Shyam Aggarwal[2] Ghanashyam Biswas[3] Seema Gulia[4] Vivek Agarwala[5] Maheboob Basade[6] P.N. Mohapatra[7] Krishna Muddu Vamshi[8] Arun Warrier[9] Krishna Prasad[10] Partha Roy[11] M.V. Chandrakant[12] Hemant Malhotra[13] Sachin Hingmire[14] Davinder Paul[15] Vashista Maniar[16] Alok Gupta[17] Soumya S. Panda[18] Aseem Samar[19] Nitesh Rohatgi[20] Satya Dattatreya[21] Manjunath Krishnamurthy[4] Raja Thirumalairaj[22]

[1] Department of Clinical Hematology, Mahatma Gandhi University of Medical Sciences and Technology, Jaipur, Rajasthan, India
[2] Department of Medical Oncology, Sir Gangaram Hospital, New Delhi, India
[3] Department of Medical Oncology, Sparsh Hospitals and Critical Care Private Ltd., Bhubaneswar, Odisha, India
[4] Department of Medical Oncology, Tata Memorial Center, Mumbai, Maharashtra, India
[5] Department of Medical Oncology, Narayana Superspeciality Hospital and Cancer Institute, Kolkata, West Bengal, India
[6] Department of Medical Oncology, Saifee Hospital, Mumbai, Maharashtra, India
[7] Department of Medical Oncology, Apollo Cancer Center, Kolkata, West Bengal, India
[8] Department of Medical Oncology, AIG Hospital, Hyderabad, Telangana, India
[9] Department of Medical Oncology, Aster Medicity, Cochin, Kerala, India
[10] Department of Medical Oncology, Mangalore Institute of Oncology, Mangalore, Karnataka, India
[11] Department of Medical Oncology, Dr. Bhubaneswar Borooah Cancer Institute, Guwahati, Assam, India
[12] Department of Medical Oncology, Narayana Hospital, Howrah, West Bengal, India
[13] Department of Medical Oncology, Mahatma Gandhi Medical College Hospital, Jaipur, Rajasthan, India
[14] Department of Medical Oncology, Deenanath Mangeshkar Hospital, Pune, Maharashtra, India
[15] Department of Medical Oncology, Fortis Hospital, Ludhiana, Punjab, India
[16] Department of Medical Oncology, Mumbai Oncocare Center, Mumbai, Maharashtra, India
[17] Department of Medical Oncology, Medanta Hospital, Lucknow, Uttar Pradesh, India
[18] Department of Medical Oncology, The Institute of Medical Sciences and Sum Hospital, Bhubaneswar, Odisha, India
[19] Department of Medical Oncology, Bhagwan Mahavir Cancer Hospital & Research Center, Jaipur, Rajasthan, India
[20] Department of Medical Oncology, Fortis Cancer Institute, Delhi, India
[21] Department of Medical Oncology, Renova Soumya Hospital, Secundarabad, Telangana, India
[22] Department of Medical Oncology, Apollo Cancer Center, Chennai, Tamil Nadu, India

Address for correspondence Purvish M. Parikh, MD, DNB, FICP, PhD, ECMO, CPI, Professor and Head of Clinical Hematology, Mahatma Gandhi University of Medical Sciences and Technology, Jaipur 302022, Rajasthan, India (e-mail: purvish1@gmail.com).

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Abstract

Purvish M. Parikh

Cancer-associated anemia (CAA) remains a major unmet need that compromises overall survival (OS) and quality of life (QoL). Currently, available guidelines do not take into consideration the unique challenges in low- and middle-income countries (LMIC). Our CAA patients have to battle preexisting impaired nutritional status, depleted body iron stores, financial limitations, and difficulty in having easily accessible affordable healthcare. Hence, we fulfilled the need of guidelines for LMIC. A group of subject experts were put together, given background literature, met in a face-to-face discussion, voted using Delphi process, and finally agreed on the contents of this guideline document. As many as 50% of cancer patients will have significant anemia (hemoglobin < 10 g/dL) at initial diagnosis. It is most commonly seen with gastrointestinal malignancies, head and neck cancers, and acute leukemias. The hemoglobin falls further after initiation of cancer directed therapy, due to chemotherapy itself or heightened nutritional deficiency. Its evaluation should include tests for complete blood count, red blood cell morphology, reticulocyte count, Coombs test, and levels of vitamin B12 and folic acid. Iron status should be monitored using test to measure serum iron, total iron binding capacity, transferring saturation, and serum ferritin levels. A minimum of 50% of cancer patients with anemia require iron supplements. The preferred mode of therapy is with intravenous (IV) iron using ferric carboxymaltose (FCM). Most patients respond satisfactorily to single dose of 1000 mg. It is also safe and does not require use of a test dose. Significant anemia is found in at least half of all cancer patients in India, South Asian Association for Regional Cooperation region, and other LMIC countries. Its awareness among healthcare professionals will prevent it from remaining undiagnosed (in up to 70% of all cancer patients) and adversely affecting OS and QoL. The benefits of treating them with IV iron therapy are quick replenishment of iron stores, hemoglobin returning to normal, better QoL, and avoiding risk of infections/reactions with blood transfusions. Many publications have proven the value of single-dose FCM in such clinical situations. CAA has been proven to be an independent prognostic factor that adversely affects both QoL and OS in cancer patients. Use of FCM as single IV dose of 1000 mg is safe and effective in the majority of patients with CAA.

Keywords

- iron deficiency
- ferric carboxymaltose
- erythropoietin
- quality of life
- well-being

Introduction

Cancer-associated anemia (CAA) is a major problem that remains largely unrecognized and therefore poorly managed. Almost 75% of all cancer patients will be found to have anemia during the course of their illness (hematological malignancies more than solid tumors). Also, the anemia will be sufficiently severe for the patient to need blood transfusion in 40% of them.[1] As far as low- and middle-income countries (LMIC), SAARC (South Asian Association for Regional Cooperation) region, and India are concerned, CAA is higher due to the prevailing underlying malnutrition in the general population and growing geriatric segment.[2–5]

In cancer, anemia occurs due to several reasons, the common ones being advancing age, nutritional deficiency, lower baseline hemoglobin (Hb), hemolysis, blood loss, infiltration of the bone marrow by tumor cells, and therapy with myelosuppressive potential (viz. chemotherapy and/or radiation therapy).[6,7] Cancer by itself also leads to anemia of chronic diseases (just like that seen with others chronic inflammatory diseases and renal failure).[8] CAA is proportional to the tumor burden/stage of cancer. It also varies with the underlying type of cancer, being highest for lung, head, and neck, and gastrointestinal (GI) cancers.[9]

Tumor cells and their microenvironment release cytokines and other inflammatory mediators that suppress erythropoiesis and reduce red blood cell (RBC) survival. They also lead to iron sequestration and impaired iron utilization (functional iron deficiency).[10] Consequences of CAA include fatigue, impaired quality of life (QoL), and limitation in mobility and physical activity.[11] It can also lead to lower response rate, disease-free survival, and overall survival (OS).[12–14]

Unmet Need

There are several guidelines published by international societies on this subject, including from American Society of Clinical Oncology (ASCO; 2010), European Society for

Medical Oncology (ESMO; 2020), National Comprehensive Cancer Network (NCCN; 2021), and European Cancer Anaemia Survey (ECAS; 2013).[15–18]

Unfortunately, their primarily focus has been on the Caucasian population from developed countries, with a bias toward the use of erythropoietin-stimulating agents (ESA) like erythropoietin (EPO) or darbepoetin and is blind to the unique circumstances faced by LMIC. Our cancer patients often have impaired nutritional status at baseline, low iron stores, financial constraints, and limited access to healthcare facilities in their neighborhood.

Safety is also of paramount importance. When data accumulated regarding the risk of thromboembolic events and mortality with the use of EPO in cancer patients, U.S. Food and Drug Administration (FDA) issued a black box warning followed by development of ESA APPRISE Oncology Program (based on the Oncology Drug Advisory Committee's recommendations and the FDA's subsequent action, training program was mandated for healthcare providers—based on Risk Information for the Safe use of ESAs)[19]

Hence, we decided to develop our own guidelines for the management of CAA for LMIC. This is also applicable to the SAARC region, and especially India.[20,21]

Methods

We established a subject expert committee that included oncologists and hematologists in clinical practice and management of CAA (all of them as co-authors).[20,22] They consist of academic organizations, corporate hospitals, and private practice from different parts of India. The first author initially had one-to-one discussion with each of them, obtained their consent to be part of the guidelines committee and took their inputs to make the draft of the discussion points. A face-to-face meeting was then conducted where there was in-depth discussion on what is relevant for CAA in India, SAARC countries, and other LMIC. The discussion was added to the draft points and circulated as clinical practice statements for approval by the expert group. After obtaining feedback from all the members, the final draft was prepared and voting conducted using Delphi method.[23] While there are specific objectives recommended in the Delphi process, various modifications of the process and parameters have evolved (*Realtime Delphi, Delphi Markets*, *Policy Delphi*, *Argumentative Delphi*, *Group Delphi technique*, etc.). Most have utilized between 2 and 5 rounds of answering. The definition of using agreement that exceeded a certain percentage cutoff value (the value from which consensus was assumed) has varied between 20 and 100% agreement. Most publications have used a threshold of more than 60%. In this report, we used the predefined cutoff at 80% to consider that the recommendation was by consensus.[23] For questions where experts had voted for "not sure" or "abstain," additional published evidence was provided to them, and they were requested to vote again for these questions. The final voting was then tabulated and used to complete the "Practical Clinical Consensus Guidelines for the Management of Cancer Associated Anemia in LMIC" manuscript.

Results

We have divided the results into five sections (►Table 1).

A. Before start of cancer directed therapy:
There was unanimous agreement (22/22; 100%) that CAA is under reported as well as not given adequate importance. Majority (18/22; 81.8%) agreed that about half the cancer patients have significant anemia (Hb < 10 g/dL) when their cancer is diagnosed. Among the cancer patients having anemia at initial presentation, 90.9% (20/22) agreed that preexisting nutritional deficiency exists and that functional iron deficiency (anemia secondary to cancer) is the cause of anemia. Among patients with solid tumor malignancies and anemia, the most site was GI tract or head and neck region was the agreement among 21/22 (95.5%) of the experts. Similarly for patients with hematological malignancies and anemia, the experts agreed that the most common association was with patients having acute leukemias (19/22; 86.4%).

B. Cancer therapy and anemia:
Experts were in agreement regarding chemotherapy being the cause of anemia in at least 20% of cases (18/22; 81.8%) and nutritional deficiency developing in at least 10% of cases (19/22; 86.4%). Among cancer patients who do not have anemia at initial presentation, and are treated with chemotherapy, at least 20% are at risk of developing severe anemia (Hb < 8 g/dL) was the unanimous opinion of the experts (22/22; 100%). Among cancer patients who do not have anemia initially and develop severe anemia (Hb < 8 g/dL) while on chemotherapy, it is usually seen after three to four cycles of chemotherapy were the majority consensus (18/22; 81.8%).

C. Implications of CAA:
The majority of experts agreed that CAA is as independent prognostic factor that adversely effects patients' OS and QoL (18/22; 81.8%).

D. Investigations of CAA:
There was unanimous consensus that all patients with CAA should be investigated with complete blood count (CBC), RBC morphology, retic count, iron monitoring panel, Coombs test, and levels of vitamin B12 plus folic acid (22/22; 100%. So, also, a 100% consensus (22/22) that iron monitoring testing needs to include serum iron, total iron binding capacity, transferrin saturation, and serum ferritin levels.

E. Treatment of CAA:
Almost all the experts (21/22; 95.5%) were of the opinion that at least 20% of cancer patients with anemia require treatment (specifically for their anemia) with additional supportive care. That at least 10% of cancer patients with anemia require treatment (specifically for their anemia) with diet changes was the opinion of the clear majority (18/22; 81.8%).

Regarding the need for erythropoiesis stimulating agents for the management of cancer related anemia, 16/22 (72.7%) experts were of the opinion that it is recommended in less

Table 1 Practical clinical consensus guidelines for the management of cancer-associated anemia (CAA) in low- and middle-income countries (LMIC)—results of voting by subject expert committee members

Sr. no.	Statement	Yes	No	Abstain/ not sure
	Before start of cancer directed therapy:			
1	CAA is both under reported and not given adequate importance	22 (100%)	0	0
2	In clinical practice, about 50% of cancer patients have significant anemia (hemoglobin [Hb] < 10 g/dL) at the time of diagnosis	18 (81.8%)	4 (18.2%)	0
3	In cancer patients with anemia, preexisting nutritional deficiency is responsible for approximately 20%	20 (90.9%)	1 (4.5%)	1 (4.5%)
4	In cancer patients with anemia, functional iron deficiency (anemia secondary to cancer) is responsible for approximately 20%	20 (90.9%)	1 (4.5%)	1 (4.5%)
5	For solid tumors, CAA is most commonly seen in patients with gastrointestinal malignancies and head and neck cancers	21 (95.5%)	0	1 (4.5%)
6	For hematological malignancies, CAA is most commonly seen in patients with acute leukemias	19 (86.4%)	2 (9.1%)	1 (4.5%)
	Cancer therapy and anemia:			
7	In cancer patients with anemia, at least 20% is caused by chemotherapy	18 (81.8%)	3 (13.6%	1 (4.5%)
8	In cancer patients with anemia, nutritional deficiency developing during treatment is responsible in at least 10%	19 (86.4%)	1 (4.5%)	2 (9.1%)
9	For cancer patients who do not have anemia at presentation, and are treated with chemotherapy, at least 20% are at risk of developing severe anemia (Hb < 8 gm/dL)	22 (100%)	0	0
10	For cancer patients who do not have anemia at presentation, and develop severe anemia (Hb < 8 gm/dL) while on chemotherapy, this is usually seen after 3 to 4 cycles of chemotherapy?	18 (81.8%)	1 (4.5%)	3 (13.6%)
	Implications of CAA:			
11	CAA is as independent prognostic factor impacting overall survival and quality of life (QoL) of cancer patients	18 (81.8%)	0	4 (18.2%)
	Investigations of CAA:			
12	CAA should be investigated with complete blood count (CBC), red blood cell (RBC) morphology, reticulocyte count, iron monitoring panel, Coombs test, and levels of vitamin B12 plus folic acid	22 (100%)	0	0
13	Iron monitoring panel testing should include serum iron, total iron binding capacity, transferrin saturation, and serum ferritin levels	22 (100%)	0	0
	Treatment of CAA:			
14	At least 20% of cancer patients with anemia require treatment (specifically for their anemia) with supportive care; yes 21 (95.5%) no 1 (4.5%)	21 (95.5%)	1 (4.5%)	0
15	At least 10% of cancer patients with anemia require treatment (specifically for their anemia) with diet changes	18 (81.8%)	3 (13.6%)	1 (4.5%)
16	Less than 5% of cancer patients with anemia require treated (specifically for their anemia) with erythropoietin (EPO)	16 (72.7%)	6 (27.3%)	0
17	At least 50% of cancer patients with anemia require treated (specifically for their anemia) with iron supplements	18 (81.8%)	2 (9.1%)	2 (9.1%)
18	Patients with CAA requiring iron therapy are best treated with parenteral iron or both (parenteral and oral iron)	22 (100%)	0	0
19	For CAA, parenteral iron recommended should be intravenous (IV) preparation	22 (100%)	0	0
20	For CAA, the preferred type of IV iron preparation is ferric carboxymaltose (FCM)	22 (100%)	0	0
21	For CAA, FCM should usually be administered in single dose of 1,000 mg (1K)	21 (95.5%)	1 (4.5%)	0

Table 1 (*Continued*)

Sr. no.	Statement	Yes	No	Abstain/ not sure
22	For CAA, optimal benefit with FCM is seen if FCM 1K treatment is initiated when Hb is less than 10 gm/dL. Yes 19 (90.9%) No 2 (9.1%)	20 (95.5%)	2 (9.1%0	0
23	For CAA, use of FCM 1K dose provides satisfactory efficacy (rise in Hb and reduction in blood transfusion requirements); yes 21 (95.5%), abstain 1 (4.5%)	21 (95.5%)	0	1 (4.5%)
24	For CAA, use of FCM 1K dose has proven to be very safe; yes 21 (95.5%), abstain 1 (4.5%)	21 (95.5%)	0	1 (4.5%)

than 5% of patients, whereas 6/22 (27.3%) felt the need in a higher number of patients.

That at least 50% of cancer patients with anemia require treatment with iron supplements was the majority consensus (18/22; 81.8%). That this iron supplement should be parenteral alone or both oral and parenteral was the unanimous consensus (22/22; 100%) of the experts. Also, there was unanimous consensus (22/22; 100%) that the parenteral iron recommended should be intravenous (IV) preparation and that too using ferric carboxymaltose (FCM). The dose of FCM recommended was single administration of 1,000 mg by 21/22 (95.5%) of the experts. That such FCM administration should be optimally done when patients Hb is less than 10 g/dL was the majority consensus of 20/22 (90.9%). The near unanimous consensus (21/22 (95.5%) of such administration of FCM leads to a rise in Hb, reduces blood transfusion requirements, and is very safe in the real world.

Discussion

There is no controversy regarding the under reporting and adequate importance given to CAA.[24] As a result many cancer patients have impaired QoL, beyond what is the impact of underlying cancer alone. Since significant anemia is seen in more than 50% of cancer patients from the word go, it represents an urgent and important unmet need in India, SAARC region, and other LMIC countries. This should be at the top of the mind of all healthcare professionals, especially while dealing with acute leukemias and cancers of GI tract or head and neck region.[25]

When chemotherapy is administered, anemia occurs/ increases in at least 20% of cancer patients. Among nonanemic patients' chemotherapy administration leads to significant anemia (Hb $<$ 8 g/dL) occurs in one out of five cases, usually after three or four cycles of therapy. In other words, more than 70% of cancer patients are at risk of reduced OS and/or QoL because of CAA.[26]

When investigations are required for CAA, tests recommended include CBC, RBC morphology, reticulocyte count, iron monitoring panel (serum iron, total iron binding capacity, transferrin saturation, and serum ferritin levels), Coombs test, and blood levels of vitamin B12 plus folic acid. This will enable accurate assessment of the likely cause of anemia and assist in its appropriate management. For example, in case investigations reveal deficiency of vitamin B12 or folic acid levels in the blood, appropriate supplements are recommended.

CAA treatment can be done using blood transfusions, ESAs, and IV iron supplementations. Outcome optimization depends on choosing the right approach, depending on the severity of anemia, its underlying cause, and various patient factors such as age, number/ severity of comorbidities, and finally the goal of treatment.[14,21,22]

The controversy regarding use of ESAs for CAA is still ongoing.[27,28] In the early 2000s, the opinion was that ESAs have an increasing role in CAA. However, there was mounting evidence of their risk (thromboembolic events and death as well as risk of stimulating cancer cells). In 2007, the led to U.S. FDA issuing a black box warning.[28] Promptly use of ESAs in cancer-related anemia fell by 30% in United States. The regulatory authorities subsequently instituted a risk evaluation and mitigation strategies to train healthcare providers regarding the risk with and appropriate use of ESA in CAA as well as renal failure patients. The decline in ESA use (ESA sales fell from 10 billion (in 2006) to less than 3 billion by 2020; Amgen data) was also as a result of availability of more effective and safer parenteral iron supplementation, which became an alternative option for managing anemia in cancer patients.

There are several advantages of iron therapy including rapidly replenishing of iron stores, recovery of hemoglobin levels, improved energy and QoL, as well as avoiding the risk associated with blood transfusions (like infection, transfusion reactions, and iron overload).[22,24,29]

Use of oral iron suffers from the disadvantages of being less effective (due to missed doses or poor absorption), GI adverse reactions, and the risk of drug–drug interactions that could affect metabolism (and hence efficacy) of other drugs. IV iron leads to faster improvement in anemia-associated symptoms, bypassing the difficulties of GI tract absorption and overcoming absolute as well as functional iron deficiency. Even the risk of allergic adverse reactions, seen with the older IV preparations, are a thing of the past.[30–35]

Among iron sucrose, ferric gluconate, ferumoxytol, and FCM groups of molecules, the main difference is in pharmacokinetics, dosing, and administration requirements.[36–38] The expert group consensus was that FCM provides the most favorable pharmacokinetics and safety profile (it is safe even in patients with history or allergy to other drugs). FCM is a complex of ferric hydroxide and carboxymaltose, which provides a controlled release of the iron molecules, thus minimizing risk of any oxidative stress and/ or other adverse effects.[39]

Its ability to be used as a rapid IV infusion (1,000 mg fixed dose in 15 minutes) without the need of a test dose makes it easily applicable in the real world. Long-lasting benefit also means there is less need for a second dose, lower utilization of healthcare infrastructure, and reduced overall cost.[40–42]

There is at least one study that prospectively evaluated the impact of IV iron FCM on the QoL of cancer patients.[43] This included solid tumor cases, with functional (ferritin < 800 ng/mL) or absolute (ferritin < 300 ng/mL) iron deficiency (transferrin saturation coefficient $<20\%$). A total of 186 patients were evaluated using the Functional Assessment of Cancer Therapy-Anemia scale (variant of the Functional Assessment of Cancer Therapy General scale specifically for anemia). With the median age being 63 years, at least half of the patients belonged to the geriatric group. Use of FCM led to significant improvement in the specific scale regarding anemia ($p < 0.001$). In addition, there was improvement in both physical well-being ($p < 0.001$) and emotional well-being ($p = 0.004$).[43]

To summarize, advantages of FCM (vs. other IV iron preparations) include high-dose efficacy, rapid infusion time, reduced need to repeat a second dose, no need for test doses, less risk adverse effects, equal safety in patients with a history of allergies, and improved QoL.[44] Having said that, FCM can still rarely cause hypersensitivity, anaphylaxis or hypotension, hives, itching, swelling, difficulty breathing, and chest pain. So, patients receiving FCM infusion should be monitored closely. Less severe and self-limiting reactions can also include arthralgia, myalgia, and injection site reactions (pain, swelling, and redness).[39–44] This is why the expert group recommends the administration of FCM only when patients' Hb is less than 10 g/dL.

Today the world is facing an increasing number of cancers among the older population (geriatric cancer patients). Such patients have significant comorbidities, polypharmacy, limited mobility, and other age-related reductions in body/organ reserve. CAA is a more significant problem in this group and hence needs special mention. If biologically fit, such patients can be treated using the above guidelines as if they were younger adults.[45] If there medical (cancer and non-cancer) status suggests a limited life expectancy, the goal of the management of CAA needs to be changed accordingly. The objective should be to preserve QoL, energy, and control symptoms as long as meaningfully possible.[46,47]

Conclusion

CAA is both under reported and not given adequate importance. As many as 50% of cancer patients will have significant anemia (Hb < 10 g/dL) at initial diagnosis. Both functional and absolute iron deficiency are common. It is most commonly seen with GI malignancies, head and neck cancers, and acute leukemias. The Hb falls further after initiation of cancer directed therapy, due to chemotherapy itself or heightened nutritional deficiency. CAA has been proven to be an independent prognostic factor that adversely affects both QoL and OS in cancer patients. Its evaluation should include tests for CBC, RBC morphology, reticulocyte count, Coombs test, and levels of vitamin B12 and folic acid. Iron status should be monitored using test to measure serum iron, total iron binding capacity, transferring saturation, and serum ferritin levels. This will also help distinguish between functional and absolute iron deficiency. A minimum of 50% of cancer patients with anemia require iron supplements. The preferred mode of therapy is with IV iron using FCM. Most patients respond satisfactorily to single dose of 1,000 mg. It is also safe and does not require use of a test dose. Such therapy has been proven to improve QoL and physical and emotional well-being. In summary, it is well established that with the use of FCM in the appropriate dose at least once, we can provide our cancer patients with a safe and effective method to increase their Hb levels, avoid the risk of blood transfusion requirements, and enhance QoL.[6,14,22,30,42,48]

Conflict of Interest

None declared.

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