Artigo de consenso

Patient Blood Management em Oncologia – é possível?

Patient Blood Management – is its application possible in oncology?

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Resumo

Patient Blood Management (PBM) é um método seguro que visa melhorar a gestão médico-cirúrgica dos doentes de modo a que o seu próprio sangue seja conservado. Cerca de 32 a 60% dos doentes oncológicos têm deficiência de ferro, a maioria tem anemia e, por isso, é importante discutir estratégias que evitem o uso excessivo de sangue e redução da progressão de tumores e recorrência do cancro. Neste artigo de posicionamento, um grupo de especialistas em conjunto com a Associação Portuguesa para o Estudo da Anemia (AWGP) discute o programa PBM em hematologia e oncologia tendo em conta diversos fatores que são atualmente utilizados para aprovar os tratamentos em uso, baseados nas últimas informações atualizadas das orientações internacionais do *National Comprehensive Cancer Network®* (NCCN).

Palavras-chave: sangue; terapias; artigo de posicionamento; oncologia

Abstract

Patient blood management (PBM) is a safe approach aiming to improve a patient's medical and surgical management in ways that boost and conserve their own blood. Approximately 32% to 60% of oncology patients have iron deficiency – the majority of whom are anaemic – therefore, it is important to discuss strategies to avoid excessive blood usage and the reduction of tumour progression and cancer recurrence. In this position paper experts together with the Anaemia Working Group Portugal discussed a PBM program in haematology and oncology, taking into account several factors that are currently used to approve the applied therapies, based on the latest reviewed information of the National Comprehensive Cancer Network®.

Keywords: *blood; therapies; position paper; oncology*

Introduction

Iron deficiency is the most common and extensive nutritional disorder in the world.[1] It is equally prevalent in industrialised and developing countries, constituting a public health condition of epidemic proportions.

The anaemia prevalence in Europe ranges from 11% to 16% for males and 15% to 28% for females. Taking into consideration the aging population, it is important to note that anaemia prevalence increases with age. Also, pre-operative anaemia prevalence is much more pronounced than in the general population.[2] A change in routine anaemia management in elective surgical patients may have a sustainable impact on improved outcomes for many patients as well as a considerable health economic improvement every year.

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Iron deficiency and anaemia reduce the work capacity of individuals and entire populations, with serious economic consequences and obstacles.

According to the World Health Organization (WHO), anaemia is defined when Hb levels are < 130 g/L in men, < 120 g/L in women and < 110 g/L in pregnant women,[1,3] with iron deficiency being one of its major causes.

In Portugal, anaemia and iron deficiency are highly prevalent and largely undiagnosed. According to the EMPIRE study, the prevalence of anaemia in Portugal was 19.9%; 84% of cases of which were previously undiagnosed.[4]

About 32% to 60% of oncology patients have iron deficiency – the majority of whom are anemic.[5,6] In this particular population of patients, anaemia has multiple causes; for example, bleeding, nutritional deficiencies or kidney failure, or it may be the result of a combination of factors.[7,8] Cancer and chemotherapy can also lead to anaemia.[9] Hence, decisions on the immediate correction of anaemia should first be based on a careful evaluation of the iron supplies, to ensure adequate iron deficiency treatment is provided. Depending on individual characteristics, the severity of the anaemia and the presence of comorbidities, the treatment approach may involve iron supplementation, erythropoietin-stimulating agents (ESAs) or packed red blood cells (PRBC) transfusion.

In 2010, the World Health Assembly (WHA) – the decision-making body of WHO – recommended the patient blood management (PBM) program to its member states.[10] The concept of PBM has practical implications in reducing blood usage, namely transfusions, improving patient outcomes and reducing hospital costs.[10]

PBM is a safe way of using medical and surgical techniques to prevent anaemia and to reduce haemorrhaging, while also improving the patient's quality of life, disease free survival and the reduction of tumour progression and cancer recurrence.[2,11]

The Society for the Advancement of Blood Management (SABM) has designed a matrix that translates to each patient as the 'decision-maker center'.[12] For each patient, there is one personalised treatment. PBM is a patient-focused approach, as it encourages discussion and explores possible management options[13] (Figure 1).

The introduction of PBM in WHO member states has resulted in successful strategies in Australia, the United States and parts of Europe.[13]

The well-established concept of PBM in other medical fields, such as surgery, might be of relevance to haematology and oncology patients.[14] This population has particular characteristics and constitutes a unique challenge. Moreover, few data on PBM are available.

The present consensus resulted from an experts' meeting at which a PBM program was discussed for possible implementation in the diagnosis and therapeutics of anaemia in oncology patients with solid tumours or lymphomas for whom chemotherapy is proposed.

Methods

The National Comprehensive Cancer Network® (NCCN) regularly updates its guidelines on chemotherapy-induced anaemia, and these were adopted as a frame of discussion by an expert group who met on 17 September 2016 in Lisbon, Portugal. This meeting was endorsed by the Anaemia Working Group Portugal (AWGP), the Portuguese Society of Oncology (SPO) and the Portuguese Association of Immuno-Hemotherapy (APIH). The aim of this meeting was to discuss a PBM program in haematology and oncology patients and review the latest version of the NCCN guidelines.[15] Following the meeting,

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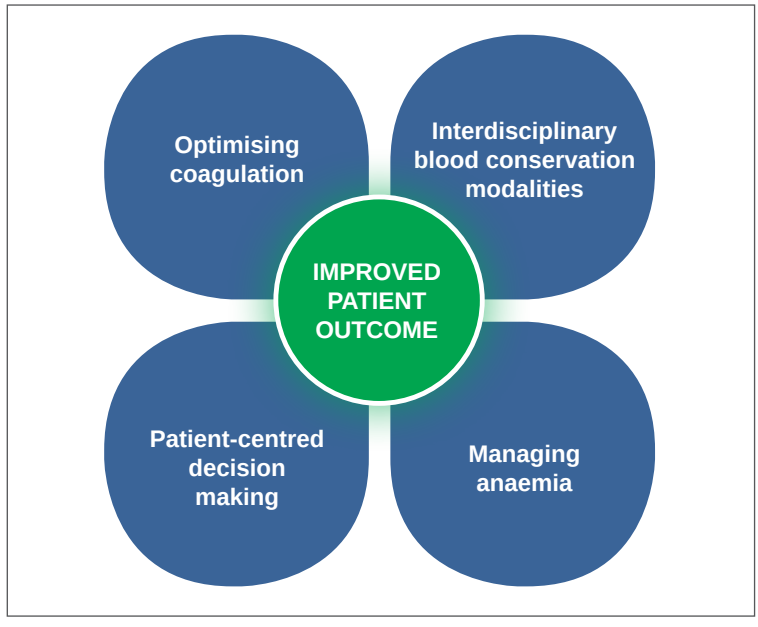


Figure 1. Patient-focused patient blood management approach (Society for the Advancement of Blood Management).[3]

all the experts reviewed the proposed consensus document on the new version of NCCN.[6]

The outcome was a Portuguese consensus document that includes recommendations for the diagnosis and treatment of anaemia and iron deficiency in patients with solid tumours or lymphomas treated with chemotherapy. All recommendations are category 2A, unless otherwise specified (based on NCCN Categories of Evidence and Consensus).[6]

Discussion

Screening evaluation

Between 32% and 60% of cancer and cancer chemotherapy patients have anaemia caused by iron deficiency, and most of these are anaemic.[5,6] In such patients, anaemia might have multiple causes (bleeding, haemolysis, hereditary disease, kidney failure or nutritional deficiency) or be the result of a combination of causes;[7,8] the disease itself or treatment can also lead to anaemia[9] (Figure 2).

Iron metabolism is a complex process in which hepcidin is the main homeostasis regulator.[16] Hepcidin is a peptide made of 25 amino acids and is upregulated in chronic inflammation scenarios, such as oncologic and autoimmune diseases, thus contributing to the development of chronic anaemia. Other factors that contribute to hepcidin upregulation include iron bioavailability, erythropoiesis and hypoxia.[16]

Bearing in mind these scenarios and the prevalence of anaemia in Portugal, the experts at the meeting concluded that anaemia and iron deficiency in oncology patients is often under-diagnosed and under-treated.

The experts agreed on the importance of proactively evaluating iron metabolism parameters in all patients with solid tumours or lymphomas, prior to chemotherapy treatment.

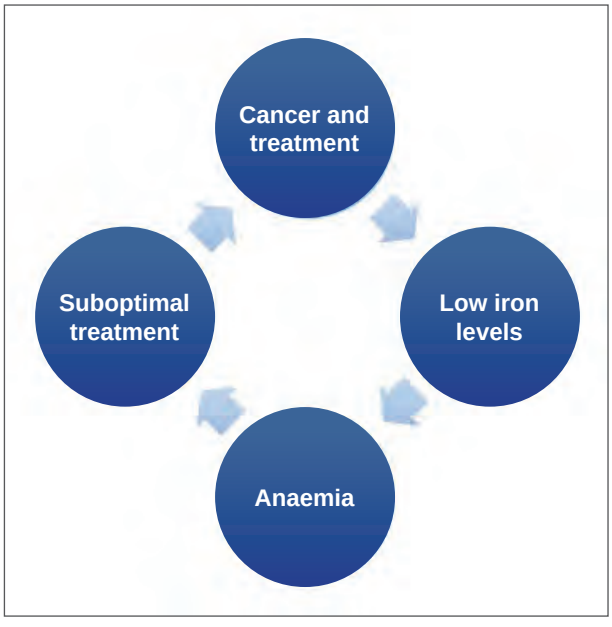


Figure 2. Anaemia cycle in a cancer patient.

When low, ferritin is diagnostic of iron deficiency. However, it is an acute phase reactant and may be falsely elevated in which case the percentage of transferrin saturation determines the need for iron.

The authors agree that the initial assessment of iron should be based on the following correct interpretations:

– Full blood count;

– Reticulocyte count (absolute number or percentage);

– Reticulocyte Hb content (CHr);

– Iron metabolism parameters (ferritin, percent transferrin saturation);

– C-reactive protein (CRP);

– Vitamin B12 and folates.

Further research is needed for hepcidin and soluble transferrin receptors as potential biomarkers for iron supplies.

Iron deficiency

Iron deficiency can be defined as absolute or functional.[17] Absolute iron deficiency occurs when iron supplies are so low that iron is not available for the production of Hb. The absence of iron compromises erythropoiesis, resulting in ferropenic anaemia.[18] Functional iron deficiency (iron restricted erythropoiesis) is defined by a low transferrin saturation with normal or high ferritin caused by the upregulation of hepcidin, which inhibits iron absorption and iron release from circulating macrophages.[17]

According to the NCCN updated guidelines (Cancer and Chemotherapy-Induced Anaemia) if the cause of anaemia is cancer-related inflammation and/or myelosuppressive chemotherapy (for solid tumours or lymphoma), it is necessary to assess the cause of anaemia in order to determine the initial treatment.[4] The authors agreed that these guidelines could be a basis for developing a national consensus document. Thus, the latest version of these guidelines was discussed at the meeting[15] and the updated NCCN guidelines were taken into account in the preparation of this document.[6] As shown in Figure 3, the following approach is proposed.

The authors also agree that all patients should have absolute or functional iron deficiency treatment and iron intravenous (IV) supplementation should be the first step in this treatment.

The various iron deficiency and anaemia treatment options are as follows:

Iron supplementation

Anaemia correction and iron supply replacement in patients with iron deficiency is achieved through iron supplementation, which can be administered orally or intravenously. In Portugal and Europe (excluding Switzerland), only 31% of oncology patients have iron supplementation treatment, most of which is delivered orally.[19]

A number of randomised studies have evaluated the efficacy of ferric carboxymaltose efficacy in treating iron-deficiency anaemia in different disease contexts.[20] According to the Summary of Product Characteristics (SmPC), ferric carboxymaltose is approved in Portugal for the treatment of iron deficiency in patients who are intolerant to, or respond poorly to, oral iron. The drug replenishes iron stores and corrects iron deficiency in various populations, including patients with chronic kidney disease, chronic heart failure, inflammatory bowel disease, intrauterine haemorrhage, postpartum anaemia or perioperative anaemia. IV ferric carboxymaltose is generally better tolerated than oral iron sulphate in patients with iron deficiency and those with or without anaemia. The most common side effects – mild to severe in intensity – are nausea, headache, dizziness, hypertension and injection site reaction.[20]

In an 8-week randomised clinical trial in patients with indolent lymphoid malignancies, the average increase in the level of Hb in those receiving ferric carboxymaltose was significantly higher than in the control group (no anaemia treatment).[21] A multicentre, non-interventional prospective study conducted in Germany, which was designed to evaluate ferric carboxymaltose use in oncology patients with anaemia and absolute or functional iron deficiency, showed that ferric carboxymaltose significantly improved Hb levels ($p < 0.0001$) from initial values.[22] A pilot study that included 64 patients with chemotherapy-related anaemia and no absolute or functional iron deficiency, who were scheduled to receive chemotherapy and darbepoetin, showed that there was no difference in the Hb response rate between IV ferric gluconate 125 mg weekly or oral iron 30 mg daily. The increase in Hb levels was similar in both arms of treatment.[23]

It was agreed that all patients with absolute and functional iron deficiency, with or without anaemia, should be treated. Although oral iron is frequently prescribed, it does not

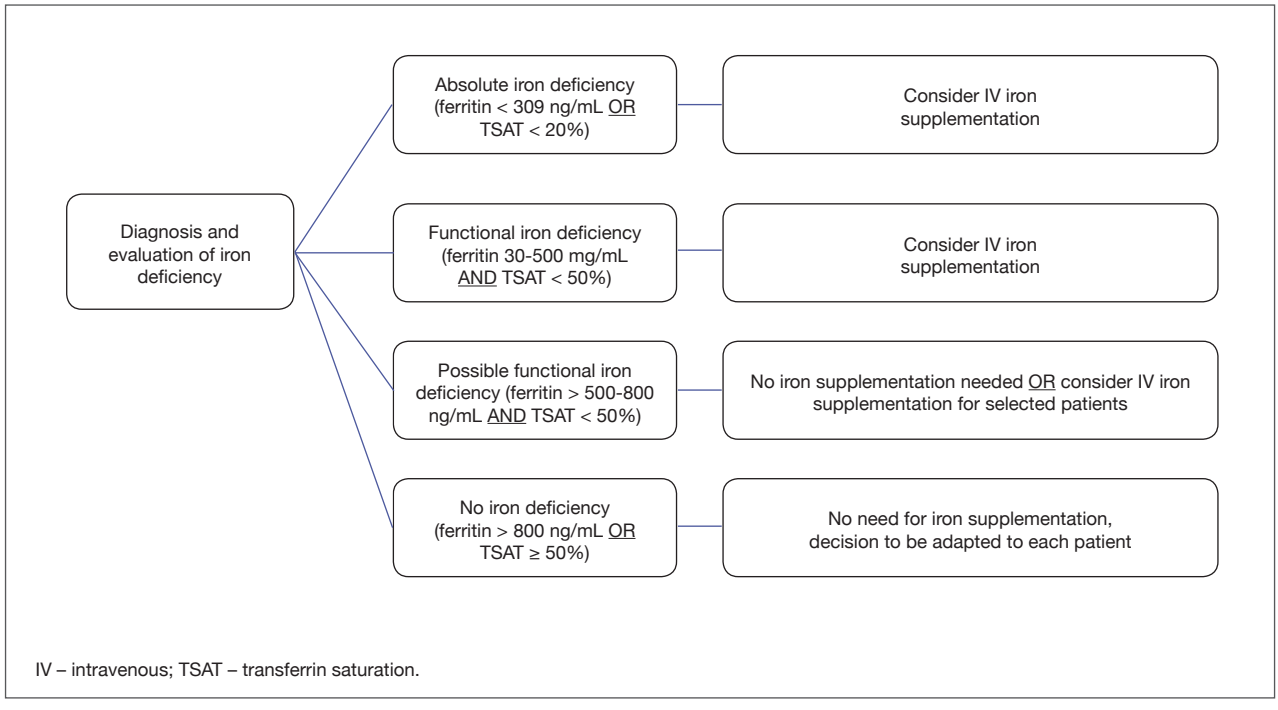


Figure 3. Evaluation and management of iron supplies in cancer patients.

provide bioavailability. The authors agree that IV iron supplementation should be considered as a first treatment, as studies suggest that this route of administration is more effective than oral iron.[4,24] The authors also agreed that IV iron supplementation is normally under-used in this population.

Erythropoietin Stimulating Agents

This therapy, whose primary purpose is to avoid transfusions, has been shown to stimulate erythropoietin in patients with low RBC levels.[4]

However, the use of ESA therapy has been associated with an increased risk of thromboembolic events and a possible increase in tumour recurrence. It also reduces progression-free survival.[3,14] Due to these risks, the US Food and Drug Administration (FDA) issued an alert in 2007 with substantial revisions of labelling that resulted in regulations on the use of ESA therapy. The FDA has been calling for a risk evaluation and mitigation strategy since 2010.

Iron deficiency can trigger thromboembolic events, some of which are associated with this therapy. Such outcomes can be prevented by conducting an iron metabolism study prior to treatment.[25]

In five published studies, the efficacy of IV iron supplementation with ESA is superior to that of oral iron and ESA alone.[19]

Therefore, the authors believe that ESA therapy should only be restricted to patients with anaemia who are receiving concomitant chemotherapy and should always be given with IV iron supplementation.

Packed red blood cell transfusion

PRBC transfusion has the advantage of offering a rapid increase in Hb and haematocrit (Hct) levels in patients who require immediate correction of anaemia.[6] However, there are some risks to this approach,[3,14] including increased risk of infections,[26] thromboembolic events and reduced progression-free survival.[14]

In patients considered for transfusion, according to Hb < 7, a restrictive strategy should be implemented, with a timely assessment of transfusion efficiency (whenever possible).

In a more logical and practical sense, safe practice requires that only one unit of PRBC should be prescribed, and monitoring maintained for 24 hours.[25,27]

The authors agree on the need to evaluate iron supplies in all patients, bearing in mind the PBM approach and considering the different forms of anaemia. The following challenges arise for oncology patients:

– Will anaemia correction have implications for the prognosis?

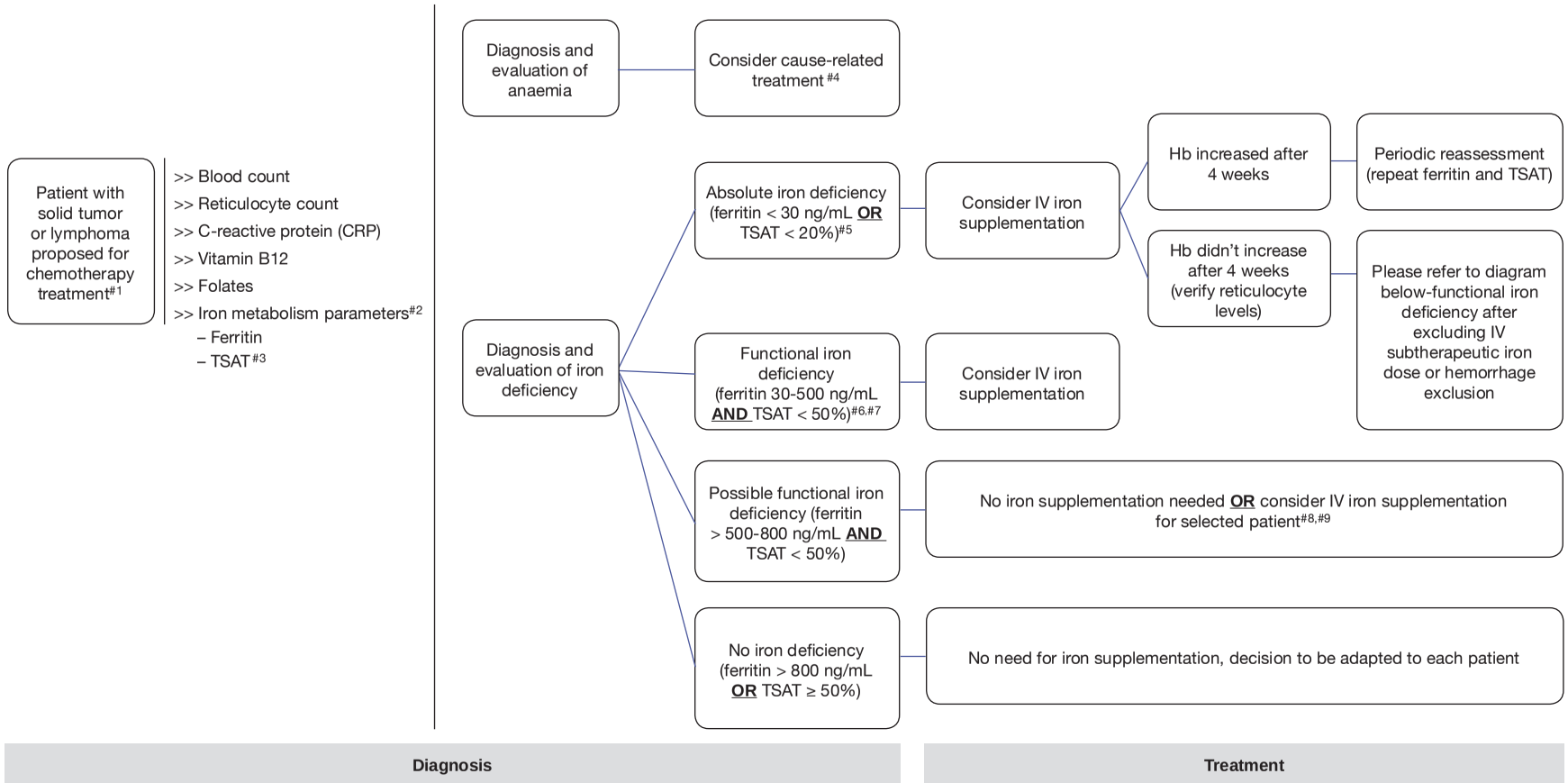
– Will progression-free survival increase?

– Will infection situations be more easily resolved?

– Could hospitalisation rates be influenced?

– Will the need for transfusions be reduced?

Following the discussion, an algorithm for the diagnosis and treatment of oncology patients with iron deficiency and anaemia was proposed (Figure 4). This algorithm resulted from an adaptation of the NCCN guidelines (Chemotherapy-Induced Anaemia) to Portuguese clinical practice. The aim is to promote early diagnosis and treatment and thus avoid allogeneic



ESA – erythropoietin-stimulating agents; Hb – haemoglobin; IV – intravenous; PRBC – packed red blood cells; TSAT – transferrin saturation.
#1 Early diagnosis and treatment to avoid allogeneic transfusions.
#2 The determination of hepcidin and soluble transferrin receptors values may be justified in the analysis of special situations.
#3 Transferrin saturation (%) = (serum ferric/total iron binding capacity) x 100.
#4 Restrictive transfusion strategy should be implemented, with a single PRBC unit and evaluation of efficiency and IV iron administration during the first 24 hours.
#5 If values of ferritin and TSAT are discordant, a low ferritin value prevails in the decision on the benefit of IV iron treatment.
#6 The use of ESA should be restricted to patients with chemotherapy-induced anaemia with no curative intent and should be concomitant with IV iron.
#7 Patients undergoing ESA therapy easily develop iron functional deficiency and may benefit from IV iron supplementation.
#8 The administration of IV iron in these patients should be individualized in order to minimize the need for allogeneic transfusion.
#9 Consider as diagnosis of exclusion anaemia/iron deficiency genetically determined refractory diagnosis.

Figure 4. Algorithm for the diagnosis and treatment of oncology patients with iron deficiency and anaemia.

transfusions in this population of patients. The first step is to perform a screening evaluation to assess the type of iron deficiency. Depending on the type of iron deficiency, a number of patient-focused treatments are proposed.

Experts also discussed the possibility of systematically recording the information obtained from the evaluation of the parameters analysed in oncology patients, for post-analysis. This could prove to be of great value in resolving such issues as: progression-free survival, global survival, time to tumour progression, global response rate, PRBC transfusions and vascular thromboembolic events.

Finally, the authors suggest that each health institution should be responsible for informing its patients on how anaemia and iron deficiency treatment can improve their quality of life.

Conclusions

Based on the expected saving of direct and indirect costs from an intelligent implementation of PBM, hospitals should support the PBM management with necessary resources.

In Portugal, the PBM concept is well established in surgical patients, demonstrating significant reductions in blood use and costs, and in improving patient quality of life. The same principles might be applied to patients with solid tumours or lymphomas proposed for chemotherapy. Thus, it is fundamental to:

– recognise and diagnose early iron deficiency and anaemia;

– assess iron supplies in all patients;

– identify vitamin B12 and folic acid deficits and correct their levels;

– treat absolute and functional iron deficiency, with or without anaemia;

– provide adequate treatment of iron deficiency through IV iron. In patients with chemotherapy-induced anaemia, with no curative intent, ESA can be used as a concomitant treatment to IV iron;

– prescribe a single PRBC with assessment of transfusion efficiency;

– implement a restrictive threshold for PRBC transfusions in agreement with national clinical recommendations and considering all applicable exceptions.

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