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Mini Review

Anemia in Metastatic Solid Tumors: A Frequent and Serious Finding. Small Review of the Literature

Youssef Jounblat and Georges El Hachem*

Department of Hematology and Medical Oncology, Institut Jules Bordet, Belgium

***Corresponding author**

Georges El Hachem, Department of Hematology and Medical Oncology, Institut Jules Bordet, Belgium, Email: georges.elhachem@bordet.be

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Abstract

Anemia is a frequent debilitating problem, negatively affecting the quality of life of cancer patients. It is associated with poor prognosis and has been directly correlated with fatigue. Despite being more common in hematologic malignancies, anemia is frequently seen in solid tumors. It is multifactorial, and is caused by the cancer itself or secondary to cytotoxic treatment. Blood transfusion used to be a primary treatment of the anemia until the era of recombinant human erythropoietin. It is essential to the cytotoxic all reversible causes, as bleeding, vitamins deficiencies and especially functional iron deficiency. Here we are writing a small review concerning the anemia in metastatic solid tumors, discussing the different etiologies, how anemia affects the prognosis and quality of life, then stressing on its adequate management. Our aim is to make clinicians more aware of this serious and common finding during the course of any metastatic solid tumor in order to improve the outcome.

INTRODUCTION

Anemia is defined as a hemoglobin (Hgb) level less than 14 g/dL in men and less than 12 g/dL in women. According to the WHO grading system, it is classified as:

- Mild anemia (grade I): Hgb level is between 10 g/dL and the normal,
- Moderate (grade II): Hgb level is between 8 and 9.9 g/dL,
- Severe (grade III): Hgb level is between 6.5 and 7.9 g/dL,
- Life threatening (grade IV): Hgb level is less than 6.5 g/dL [1].

Pathophysiology

The origin of anemia in cancer patients is often multifactorial with three main responsible mechanisms: blood loss, increased destruction of red blood cells (RBCs) and decreased production of functional RBCs [2]. Other conditions may worsen these mechanisms creating a vicious circle: renal failure, nutritional deficiencies (especially folate and B12 deficiency), coagulopathies and severe inflammatory processes [3] (Figure 1). The cancer itself may act directly on the bone marrow by invasion and metastasis leading to suppression of erythropoiesis or indirectly through cytokine release leading to iron sequestration and dyserythropoiesis [2,3]. Furthermore, cytotoxic chemotherapy

may worsen the anemia either by impairing erythropoiesis or by its nephrotoxic effect added to the myelotoxicity that accumulates over the course of the treatment. Among chemotherapeutic agents, platinum based regimen and taxanes were most commonly associated with grade III-IV anemias [4]. Moreover, cytokine overproduction alters the iron availability for erythropoiesis leading to an entity called functional iron deficiency (FID). FID is defined as serum transferrin saturation less than 20 % or ferritin less than 100 ng/mL [5].

Prevalence

Between the metastatic solid tumors, anemia is mainly seen in gynecologic malignancies (49%), colo-rectal cancers (39%), lung cancer (38%), breast cancer (30%) and uro-genital malignancies (29%). It is either caused by the inflammatory process related to the disease itself, the resulting complications or secondary to chemotherapeutic regimen using platinum or other myelotoxic agents [6]. Ludwig et al., analyzed the cancer patients according to their anti-tumoral treatment and found that anemia was seen in 75 % of patients treated with chemotherapy, in 72 % of patients treated with combined chemo-radiation therapy, in 62 % of those who received concomitant chemo-radiation therapy and in 38 % of those who only received radiotherapy. Xu H et al., confirmed these findings with a considerably high incidence of moderate to severe anemia (Hgb less than 10 g/dL) in patients with solid tumors receiving chemotherapy [7].

Consequences of anemia

The abnormal reduction in RBCs and the resultant decrease in Hgb lead to a reduction in the oxygen-carrying capacity of the blood. In turn, it will lead to patient weakness, pallor, dyspnea, and most commonly, fatigue. Anemia is highly associated with

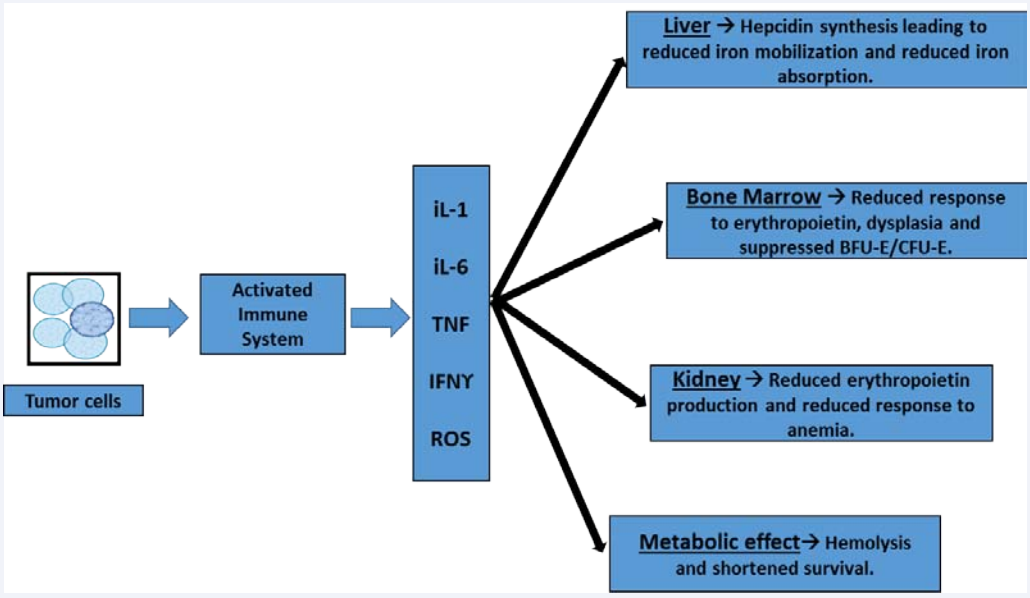

Figure 1 Pathophysiology of cancer related anemia.
Abbreviations: iL-1: interleukin-1; iL-6: interleukin-6; TNF: Tumor Necrosis Factor; IFNY: Interferon Gamma; ROS: Reactive Oxygen Species

fatigue and worsening of the quality of life (QOL). Crawford et al., confirmed this correlation by demonstrating a change in the linear analog scale assessment (LASA) score with hemoglobin level. Thus, there was a direct relationship between increases in Hgb levels in a range from 8-14g/dL and improvements in QOL. However, the largest incremental gain in QOL occurred with an increase of the Hgb from 11g/dL to 12 g/dL [8]. Hence, Z. Butt and D. Cella reported that Hgb level was the only significant predictor of fatigue in anemic cancer patients [9].

TREATMENT

Before initiating any treatment, a thorough evaluation of the contributing and aggravating factors should be done. Therapeutic options may vary widely depending on the etiology and severity of the anemia.

Blood transfusions are the fastest way for short term increase of the hemoglobin level. They rapidly reduce anemia related symptoms, but do not address its underlying cause. Pure red blood cells (PRBC) transfusions are rarely indicated if Hgb is more than 10 g/dL. According to the American Association of Blood Banks (AABB), the recommendations for PRBC transfusions are the following:

- A Hgb level of 7 g/dL as a threshold for hospitalized patients who are hemodynamically stable,

- A Hgb level less than 8 g/dL for symptomatic hospitalized patients with a pre-existing cardiovascular disease.

Therefore, clinicians should make transfusion decisions for all patients based on symptoms as well as Hgb levels [10].

However, blood transfusions are associated with many serious reactions, infectious complications and increased risk of thromboembolic events. Increased risk of in-hospital mortality was also reported in the literature [11].

Compared with blood transfusions, Erythropoiesis Stimulating Agents (ESAs) take weeks to elicit a Hgb response by stimulating erythropoiesis in a similar physiologic mechanism. Thus, they boost the reduced erythropoietin (EPO) levels and overcome the acquired resistance secondary to inflammatory cytokines (Figure 1). It is essential to correct the additional causes of anemia prior to the initiation of EPO: iron and other vitamins deficiencies, nutritional defects, hemolysis and bleeding. ESAs decrease the anemia related symptoms and help in decreasing transfusion requirements in patients with metastatic solid tumors receiving chemotherapy. In a randomized controlled trial, Little wood et al. showed that Epoetin alfa reduced the transfusion requirements in anemic patients receiving chemotherapy compared with placebo (24.7% vs 39.5%, p= 0.0057), and there was an increase in Hgb level (increase of 2.2g/dL vs 0.5 g/dL, respectively; $p < 0.001$) associated with an improvement of QOL [12]. Nevertheless, ESAs carry a lot of known risks and complications when targeting a Hgb above 12 g/dL: the Cochrane review of 91 trials with 20,102 participants, done in 2012, showed an increased risk of venous thromboembolism (VTE) in patients treated by ESAs, as well as a strong evidence of increased mortality during active therapy and a modest evidence towards increasing overall mortality [13]. Similar results were seen in a meta-analysis, conducted by the Agency for Healthcare Research and Quality's (AHRQ) in 2013, by combining results from 31 trials of EPO versus control and 6 trials of Darbepoetin versus control [14].

Other individually controlled trials showed that ESA may adversely affect the survival in certain cancer patient populations: head and neck cancer patients receiving exclusive radiation therapy (RT) and non-small cell lung cancer patients not treated with neither chemotherapy nor RT [15].

Another randomized phase 3 trial done in 2015 by Shenouda G et al., assessed the effect of EPO on the loco-regional control in anemic patients treated with radiation therapy for squamous cell

carcinoma of the head and neck. It also showed non encouraging results concerning the use of ESAs in terms of tumor progression and affected survival [16]. Besides, current ESA labels and clinical guidelines of European Medicines Agency (EMA), FDA, ASCO/ASH, and NCCN, continue to recommend avoidance of ESAs when ''cure'' is the goal of therapy due to lingering concerns about an adverse effect on disease outcomes [17,18].

As seen above, FID is a major contributor to hypo-proliferative erythropoiesis. Consequently, iron supplementation is a cornerstone in the treatment of cancer related anemia. Increased hepcidin level limits the availability of oral iron preparation. Thus, intravenous iron is more efficient specially when administered with EPO, with 50 to 70 % response rate and correction of anemia, improvement of the QOL and reduction of the transfusion requirements [12,19].

CONCLUSION

To conclude, anemia is frequently seen in metastatic solid tumors. It impairs the patient's functional status, and causes fatigue that can be disabling. Anemia has been linked to adverse prognosis and poor outcome. Clinicians and oncologists should be aware of cancer related anemia. Its correction improves QOL. It is multifactorial, thus full history and laboratory work up are essential to rule out reversible etiologies. If the patients are symptomatic and require a rapid hemoglobin correction, PRBC transfusion remains the mainstay acute short term treatment. However, chronic cancer related anemia should be treated with ESAs taking into consideration the FID.

REFERENCES

1. NCCN clinical practice guidelines. Cancer and chemotherapy-induced anemia.
2. Adamson JW. The anemia of inflammation/malignancy: mechanism and management. Hematology Am Soc Hematol Educ Program. 2008; 159-165.
3. Steensma DP. Is anemia of cancer different from chemotherapy-induced anemia? J Clin Oncol. 2008; 26: 1022-1024.
4. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. J Natl Cancer Inst. 1999; 91: 1616-1634.
5. Auerbach M, Ballard H, Trout JR, McIlwain M, Ackerman A, Bahrain H, et al. Intravenous iron optimizes the response to recombinant human erythropoietin in cancer patients with chemotherapy-related anemia: a multicenter, open-label, randomized trial. J Clin Oncol. 2004; 22: 1301-1307.
6. Ludwig H, Van Belle S, Barrett-Lee P, Birgegård G, Bokemeyer C, Gascón P, et al. The European Cancer Anaemia Survey (ECAS): a large, multinational, prospective survey defining the prevalence, incidence, and treatment of anaemia in cancer patients. Eur J Cancer. 2004; 40: 2293-2306.
7. Xu H, Xu L, Page JH, Cannavale K, Sattayapiwat O, Rodriguez R, et al. Incidence of anemia in patients diagnosed with solid tumors receiving chemotherapy, 2010-2013. Clin Epidemiol. 2016; 8: 61-71.
8. Crawford J, Cella D, Cleeland CS, Cremieux PY, Demetri GD, Sarokhan BJ, et al. Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetinalfa therapy. Cancer. 2002; 95: 888-895.
9. Cella D, Kallich J, McDermott A, Xu X. The longitudinal relationship of hemoglobin, fatigue and quality of life in anemic cancer patients: results from five randomized clinical trials. Ann Oncol. 2004; 15: 979-986.
10. Carson JL, Grossman BJ, Kleinman S, Tinmouth AT, Marques MB, Fung MK, et al. Red blood cell transfusion: a clinical practice guideline from the AABB*. Ann Intern Med. 2012; 157: 49-58.
11. Khorana AA, Francis CW, Blumberg N, Culakova E, Refaai MA, Lyman GH. Blood transfusions, thrombosis, and mortality in hospitalized patients with cancer. Arch Intern Med. 2008; 168: 2377-2381.
12. Littlewood TJ, Bajetta E, Nortier JW, Vercammen E, Rapoport B, Epoetin Alfa Study Group. Effects of epoetinalfa on hematologic parameters and quality of life in cancer patients receiving nonplatinum chemotherapy: results of a randomized, double-blind, placebo-controlled trial. J Clin Oncol. 2001; 19: 2865-2874.
13. Tonia T, Mettler A, Robert N, Schwarzer G, Seidenfeld J, Weingart O, et al. Erythropoietin or darbepoetin for patients with cancer. Cochrane Database Syst Rev. 2012; 12: CD003407.
14. Grant MD. Comparative Effectiveness Review Number 113: Epoetin and Darbepoetin for Managing Anemia in Patients Undergoing Cancer Treatment: Comparative Effectiveness Update.
15. Henke M, Laszig R, Rübe C, Schäfer U, Haase KD, Schilcher B, et al. Erythropoietin to treat head and neck cancer patients with anaemia undergoing radiotherapy: randomised, double-blind, placebo-controlled trial. Lancet. 2003; 362: 1255-1260.
16. Shenouda G, Zhang Q, Ang KK, Machtay M, Parliament MB, Hershock D, et al. Long-term results of radiation therapy oncology group 9903: a randomized phase 3 trial to assess the effect of erythropoietin on local-regional control in anemic patients treated with radiation therapy for squamous cell carcinoma of the head and neck. Int J Radiat Oncol Biol Phys. 2015; 91: 907-915.
17. Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Arcasoy MO, Spivak JL, et al. American Society of Hematology/American Society of Clinical Oncology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. Blood. 2010; 116: 4045-4059.
18. Rizzo JD, Brouwers M, Hurley P, Seidenfeld J, Arcasoy MO, Spivak JL, et al. American Society of Clinical Oncology/American Society of Hematology clinical practice guideline update on the use of epoetin and darbepoetin in adult patients with cancer. J Clin Oncol. 2010; 28: 4996-5010.
19. Goodnough LT, Nemeth E, Ganz T. Detection, evaluation, and management of iron-restricted erythropoiesis. Blood. 2010; 116: 4754-4761.

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