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Anemia Correction: Small Step towards Survival in Cancer patients

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Abstract

Anemia, characterized by hemoglobin levels below 12 gm/dl, is a prevalent comorbidity in cancer patients, with a reported prevalence ranging from 46.5% to 61% in India. Anemia induces tumor hypoxia, angiogenesis, and resistance to conventional chemotherapy and radiotherapy, presenting a barrier to effective cancer treatment. Evidence suggests that correcting anemia can enhance hemoglobin levels, reduce transfusion requirements, and improve quality of life. Anemia consistently correlates with shorter survival times across various cancers, emphasizing its role as an independent risk factor. The article highlights the associations between pretreatment and preoperative anemia and poor survival outcomes in cancer patients undergoing different treatments. The impact of anemia on radiotherapy and chemotherapy outcomes is discussed, emphasizing its correlation with reduced survival and local control. This communication highlights the significance of addressing anemia for improved disease-free survival in specific cancer types. In conclusion, anemia emerges as a detrimental prognostic factor in cancer patients, impacting survival, quality of life, and treatment efficacy. Appropriate interventions for anemia associated with iron deficiency in eligible cancer patients may contribute to improving overall survival outcomes.

Keywords: Anemia; Survival; Cancer patients; Chemotherapy; Radiotherapy.

Introduction

Anemia, defined by hemoglobin less than 12gm/dl, is a frequent comorbidity associated with cancer [1]. The prevalence of anemia in cancer patients reported from studies in India varies from 46.5% to 61% [2-4]. Multiple factors contribute to cancer-related anemia, including cancer-associated inflammation, blood loss, phlebotomy, surgical procedure, marrow infiltration, and myelosuppressive treatments, including existing nutritional deficiency [5]. Overall survival (OS) is the gold standard endpoint in oncology clinical trials, and improving survival is the end goal as cancer-associated anemia independently worsens quality of life (QoL) and OS in cancer patients [6]. While newer targeted therapies, immunotherapies, advances in radiotherapy and other advances in oncology like gene based treatment continue to contribute to survival advantages [7] some basic work-ups in cancer patients can help improve survival goals Correcting anemia represents such a crucial step in enhancing survival outcomes among cancer patients. Literature evidence suggests that treating anemia can increase hemoglobin levels, reduce transfusion requirements, and improve quality of life [8, 9].

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Anemia is barrier to cancer treatment

In Cancer patients, contexts, anemia has been postulated to instigate tumor hypoxia, angiogenesis, and confer resistance to conventional chemotherapy and radiotherapy modalities. The hypoxic milieu induced by anemia may downregulate tumor control mechanisms, a phenomenon intricately associated with the activation of hypoxia-inducible factor 1alpha (HIF-1α). HIF activation, triggered by hypoxia, contributes to tumor aggressiveness and metastasis [10]. In well-oxygenated conditions, HIF-1-alpha binds to the ubiquitin proteasomal system via product of the von Hippel Lindau tumor suppressor gene (pVHL), leading to rapid degradation within 5 minutes of reoxygenation. In response to hypoxia, cancer cell metabolism is altered to induce quiescence and reduce cell division, limiting the effectiveness of oxygen-dependent cytotoxic chemotherapy, which poses a challenge for many chemotherapy regimens [11]. Tumor growth relies on angiogenesis, facilitated by VEGF interacting with receptors to induce cellular responses like proliferation and migration. Anemia, by increasing tumor cell hypoxia, may alter cancer behavior and counteract targeted therapies' efficacy. Besides the VEGF axis, hypoxic stress induces other factors like cyclooxygenase-2, connective tissue growth factor, and interleukin-8, promoting angiogenesis and a more malignant phenotype [12]. Hypoxic stress may also interfere with the efficacy of newer targeted anticancer therapies involving EGFR, HER2/neu, and antiangiogenetic treatments. The efficacy of radiation therapy in eliminating malignant cells heavily relies on the presence of molecular oxygen within tumors, which serves as a potent radiosensitizer inducing DNA damage. The intertumoral oxygen level is a key factor in determining the response to ionizing radiation therapy, with hypoxic cells being two to three times more resistant than those with normal oxygen levels. Hypoxic environments, while allowing malignant cells to survive and maintain clonogenic potential, also confer relative protection from radiation therapy, enabling surviving cells to reestablish tumors [13].

Anemia affects survival.

Anemia is consistently associated with shorter survival times in various cancers, such as lung, cervix, head and neck, prostate, lymphoma, and multiple myeloma. Studies consistently show reduced median survival (4 to 96 months) for anemic patients compared to non-anemic counterparts. A comprehensive review of 60 studies that reported the survival according to the presence or not of anemia revealed a 65% increased mortality risk in cancer patients with anemia compared to those without, varying from 19% in lung neoplasia to nearly 75% in head and neck carcinoma or lymphoma [14]. Baseline anemia emerged as a significant predictor of poor OS in EGFR-mutated NSCLC patients undergoing targeted therapy. In a study of 2,029 EGFR-mutated NSCLC patients treated with TKIs, 24.6% had baseline anemia. Those without baseline anemia had longer median overall survival (36.10 vs 29.10 months, $P=0.001$). Grade <2 anemia also correlated with longer median OS compared to grade ≥ 2 (35.00 vs 25.10 months, $P<0.001$) [15]. In anemic patients, both iron deficiency (ID) and functional iron deficiency (FID were reported to be linked to a increased risk of mortality (HR 1.51; p = 0.0065 and HR 1.73; p = 0.0007, respectively). Conversely, in non-anemic patients, FID was independently associated with improved survival (HR 0.65; p = 0.0495) [16]. Investigation of the impact of IDA on disease-free survival in colon cancer showed that IDA is associated with a less favorable long-term outcome in terms of the recurrence or progression of colon cancer, specifically in T3N0M0 stage patients [17]. Correction of hemoglobin levels reduced risk of dying by 69% in cancer patients receiving nonplatinum chemotherapy [18].

Pretreatment anemia and impact on survival

The association of pretreatment anemia with poor survival has been well-studied. A retrospective study by Huang et al [19]. evaluated the effect of pretreatment baseline anemia as a risk factor for overall survival in advanced NSCLC patients. Out of 758 patients included in the study, 27.7% have baseline anemia. After propensity score matching, anemia was a significant risk predictor of OS for advanced NSCLC patients (HR:1.6, 95% CI:1.2–2.2; p=0.003). 1g/dL decrease in Hb level increased risk of death by 10%. Non anemic patients had 7-month higher survival than anemic cohort (17.8 months; 95% CI: 16.0–23.3 months vs 10.9 months; 95%CI: 8.8–12.9 months) (p <0.001). Another retrospective study [20] published in Journal of Thoracic Oncology evaluated association of pretreatment hemoglobin with local, regional, distant control, disease-free survival (DFS) and overall survival in patients of Stage I non-small cell lung cancer undergoing treatment with stereotactic body radiation therapy (SBRT). Out of 147 patients treated between 2009 to 2014, 29% had hemoglobin less than 12 gm/dl. On multivariate analysis, a significant association was found between pretreatment anemia and regional control, disease-free survival, and overall survival (p = 0.02, p = 0.03, p = 0.05, respectively). Patients with Hb less than 12.2 gm/dl had 3-year disease-free survival and regional control rate of 70% & % 75 % respectively compared to 94% and 95% respectively in those with higher Hb levels. No association was observed on local or distant control. Authors postulated that pretreatment anemia can be related to baseline aggressive disease since ROC analysis predicted disease progression in anemic (Hb less than 12.2) patients. Similar study from Japan [21] in early stage NSCLC patients undergoing SBRT (n=77) identified anemia to be only significant prognostic factor for predicting OS (p = 0.02469). Higher 1- and 2-year OS rates were observed with higher Hb group (96.1% and

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88.3%) compared to anemic group (84.4% and 76.0%). Authors emphasized the high utility of pretreatment Hb as a predictive prognostic indicator in this treatment setting. These data emphasize that baseline pretreatment anemia is an independent risk factor for patient survival.

Preoperative anemia and impact on survival

Association between presurgical anemia in patients undergoing cancer surgery and its impact of outcomes have been studied in patients with lung, colorectal, breast cancer. In a recently published retrospective study from North West Thoracic Surgery Collaborative (NWTSC) group in England [22] evaluated the impact of preoperative anemia on short term (i.e the 90-day mortality) and long-term survival outcomes in substantial cohort of patients undergoing lung cancer resection (n= 5039). 24.0% (n = 1207) of patients were anemic. While no difference was found in short term survival outcomes in anemic patients, preoperative anemia was independently associated with reduced overall survival (HR 1.287, 95% confidence interval 1.141-1.451, p < 0.001). IVICA trial [23] explored long term outcomes of patients with colorectal cancer receiving iron replacement. Patients were randomly assigned to receive iron supplementation via either oral or intravenous (i.e.) administration prior to their elective surgery. At median follow up duration of 61 months, although there was no significant difference in 5-year overall survival between oral and intravenous iron, a pooled analysis of treatment groups on multivariate analysis found that preoperative resolution of anemia led to improved 5-year overall survival (HR 3.38, 95% CI 1.07-11.56, P = 0.044) with preference towards i.e. replacement. Another study [24] in group of operable rectal cancer patients (n=144) reported three times higher mortality risk in patients with preoperative anemia, with higher risk in higher Dukes tumor stage and older age. The effect of preoperative anemia was evaluated in breast cancer patients. Zhang et al [25] conducted a retrospective study in 2123 patients (anemic group n = 535 and a nonanemic group n = 1588) with breast cancer who underwent surgery between 2002 and 2008 to evaluate effects of anemia on efficacy parameters including overall survival. A statistically significant difference (P < 0.001) in mortality was observed between the anemic group (24.5%) and the nonanemic group (7.7%). Similarly, significant differences were also observed in various other efficacy parameters like local relapse, lymph node metastasis, and distant metastasis. Breast cancer anemic patients had a 4.939-fold increased relative risk of developing local relapse, 5.160-fold increased relative risk of developing lymph node metastasis, 3.192-fold, and 2.849-fold higher relative risk of developing distant metastasis and death. Association was observed across all stages of the disease including patients with mild anemia, defined as hemoglobin between 9-12 gm/dl, where survival was shorter. In a similar study by Kandemir et al, 23.5% (79/336) women with early-stage breast cancer who had pre-treatment hemoglobin less than < 12 g/dl, anemia was significant prognostic factor for disease-free survival and overall survival with relative risk of 1.884 and 1.785, respectively [26]. Recent FIT trial evaluated Ferric carboxymaltose infusion versus oral iron supplementation in colorectal cancer patients to improve preoperative hemoglobin levels and iron stores, together with clinical outcome variables (e.g., complications, reinterventions, and postoperative stay). Results indicate that neither intravenous nor oral iron achieves normalization of hemoglobin levels just before surgery. However, intravenous iron effectively reversed iron deficiency. In patients with mild anemia, postoperative interventions and intensive care admissions were lower with intravenous iron, emphasizing the importance of sufficient iron stores over hemoglobin levels [27]. In an Indian Phase III trial, adult cancer patients undergoing chemotherapy without erythropoiesis stimulating agents (ESA) had survival as secondary endpoint. Study showed a median overall survival of 16 months (IV iron sucrose, 95% CI: 7.3–24.7) and 20 months (oral iron ferrous sulphate, 95% CI: 11.7–28.4; SE: 4.3) with p-value of 0.73 [28].

Impact of anemia on radiotherapy and chemotherapy outcomes.

The clinical importance of pretreatment anemia, identified since the 1940s in cervical cancer patients undergoing radiation therapy [29], have been extensively documented. Anemia strongly correlates with local control and survival in squamous cell carcinoma of head and neck (HNSCC) concurrent chemoradiotherapy, as demonstrated by a significant dose-effect relationship based on Hb concentration (<120, 120–140, >140 g/L) (p=0.04). This impact on locoregional control and survival is observed not only in HNSCC or uterine cervix but also in diverse solid tumors [30]. Higher minimum hemoglobin levels during chemotherapy were associated with improved disease-free and overall survival in breast cancer patients [31]. In a retrospective analysis of adjuvant chemotherapy arm of prospective, randomized, multicenter, phase III (ABCSG Trial 5) that compared effectiveness of endocrine treatment with standard chemotherapy regimens in endocrine-responsive, premenopausal women with breast cancer, Dubsky et al [32] concluded that those who developed anemia during chemotherapy had worse local relapse free survival (LFRS). Out of 424 patients analyzed in chemotherapy arm of this trial, 77 (18.2%) developed anemia during chemotherapy. 6.9% of nonanemic patients had local relapse compared to 19.5% of anemic group (P = 0.0006) which translated to 2.96-fold increase relapse risk. Authors concluded that treatment associated anemia i.e. anemia during adjuvant chemotherapy in early breast cancer can play an important role in efficacy results of a study. This may emphasize the need to investigate the cause and treat anemia during or before chemotherapy.

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Conclusion

Anemia is now acknowledged as a detrimental prognostic and predictive factor in cancer patients receiving chemotherapy, radiation, or a combination. Studies demonstrate associations between anemia and reduced survival times in diverse solid tumors and hematologic malignancies. Evidence now clearly emphasizes its adverse effects on quality of life and functional status including survival, especially when hemoglobin levels dip below 11 g/dL. A rehabilitation program for i.e. iron (FCM) undergoing cancer surgery as suggested by the FIT trial should be explored. Timely and effective universal intervention for treatment of anemia associated with iron deficiency in all eligible cancer patients can potentially be a small step in improving patient survival outcomes.

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