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What is the value of hemoglobin as a prognostic and predictive factor in cancer?

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Abstract

Anemia is a frequently encountered complication in cancer, and is associated with fatigue and reduced quality of life. Retrospective analyses of data from patients with hematological malignancies and solid tumors provide evidence that a low baseline hemoglobin (Hb) level is a prognostic factor for poor outcome. Moreover, in some situations, low Hb is a negative predictive parameter in chemotherapy. The adverse impact of anemia has been documented in patients with lymphomas and leukemias, as well as in those with non–small-cell lung cancer, ovarian cancer, cervical cancer, renal cell carcinoma, head and neck cancer and other solid tumors. Studies in animal models support the role of low Hb levels as a negative prognostic and predictive factor. Although prospective clinical trials are still needed to confirm that Hb levels affect outcome, the available evidence suggests that there is more than one reason to pay attention to Hb levels in cancer patients: increasing Hb not only corrects anemia and thereby improves physical functioning and quality of life, but also may improve clinical outcomes.

Keywords: Anemia; Cancer; Hemoglobin; Prognostic; Predictive

1. Introduction

The ultimate goal in cancer treatment is to cure the disease, but when this is not possible, the goal becomes providing the best palliation. The most important outcomes of treatment are overall survival (OS) and disease-free survival (DFS). However, longer progression-free survival (PFS), increased response rates and improved quality of life (QOL) are also important benefits of palliative cancer therapy. These outcomes are influenced by various baseline parameters that are typically related to the patient, such as performance status, or related to the tumor, such as its histology. However, the specific and dominant factors that influence outcome in individual patients are often unclear.

Prognostic factors are variables that independently influence outcome, whereas predictive factors are those that independently influence the response to a certain intervention. Because prognostic factors suggest the future course of disease, they are often helpful in making treatment decisions. Moreover, prognostic factors are useful in the design and analysis of clinical trials, and are often used as a basis for stratification procedures. In this paper, the value of hemoglobin (Hb) level as a prognostic and/or predictive factor will be considered.

Anemia is a frequently encountered complication in cancer, and may arise as a direct effect of the malignancy or its treatment [1]. Anemia due to the cancer itself, categorized as anemia of chronic disease, is often seen before or at diagnosis of the underlying cancer and may precede the start of myelosuppressive radiation therapy or chemotherapy [2,3]. Chronic anemia of cancer may develop as a result of disease-stimulated production of inflammatory cytokines (e.g. interferons, interleukin-1, tumor necrosis factor) [1–4]. Overproduction of cytokines can inhibit erythropoiesis by reducing erythropoietin production and the responsiveness of erythroid progenitor cells, shortening the life span of red blood cells, and impairing iron utilization. Other possible causes of chronic anemia of cancer include mechanical displacement of normal erythropoietic bone marrow by tumor tissue, marrow necrosis, amyloid disposition in the bone marrow and blood

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loss or bleeding in the tumor, among others. Cancer treatment may exacerbate this type of anemia or may be the sole cause of anemia in cancer patients. Although low Hb levels are strongly associated with disease-related fatigue and decreased QOL, the relationship between anemia and cancer is complex and less well understood.

An increasing body of evidence obtained over the last decade suggests that anemia is correlated with poor clinical outcome in cancer patients [5]. Studies show that tumor hypoxia contributes to more aggressive behavior of cancer cells and may compromise the response to cancer treatment [6–9].

2. Hemoglobin level as a prognostic factor in hematological malignancies

2.1. Non-Hodgkin's lymphoma

Anemia occurs frequently in patients with non-Hodgkin's lymphoma (NHL). A retrospective analysis of 1077 patients in France with various histological NHL subtypes, most commonly diffuse–large-cell lymphoma (40%) and follicular lymphoma (19%), found anemia to be present in 341 (32%) patients before treatment was started [10]. In this study, anemia was defined as an Hb level $\leqslant$12 g/dl in all men and in women over 50 years, and a level $\leqslant$11 g/dl in women under 50 years. The incidence of anemia varied according to the NHL histology, being highest in those with diffuse–large-cell lymphoma (39%) and lowest in those with follicular lymphoma (17%). Moreover, the incidence of anemia was higher in patients with bone marrow involvement than in those without (37% versus 27%, respectively, $P=0.0005$).

In a univariate analysis of data from this study, anemia was an adverse prognostic factor for both OS and PFS ($P<0.0001$) [10]. Median OS was 47 and 146 months in patients with anemia and those with normal Hb levels, respectively, whereas median PFS was 15 and 64 months, respectively. Anemia was associated with shorter OS in all histological subtypes except marginal zone lymphoma. Anemia remained a significant adverse prognostic factor for OS and PFS in the multivariate analysis for the population as a whole ($P=0.0001$ and $P=0.0048$, respectively), and for those with bone marrow involvement ($P=0.007$ and $P=0.005$, respectively), but not for those without bone marrow involvement. Notably, addition of anemia to the International Prognostic Index (IPI) significantly improved the prognostic significance of this index for OS and PFS (both $P=0.0004$).

In contrast, in a recent retrospective analysis of 987 follicular lymphoma patients in Italy, only 8% had low Hb levels (<12 g/dl for men and <10 g/dl for women) before the start of treatment [11]. Patients received a variety of treatments (e.g. single-agent chemotherapy with or without α-interferon, multi-agent chemotherapy, radiation therapy alone, no initial therapy). In the univariate analysis, low Hb levels, compared with higher Hb levels, were associated with poorer 5-year (60% versus 83%, respectively) and 10-year (53% versus 65%, respectively) survival rates ($P=0.0001$). Of the 11 variables significantly associated with poorer outcome in the univariate analysis, only six proved to be significant in the multivariate analysis: age >60 years, male gender, number of extranodal sites (two or more), B symptoms (unexplained high temperature, heavy night sweats, and loss of >10% of total body weight), elevated serum lactate dehydrogenase (LDH) levels, and high erythrocyte sedimentation rate (ESR). Using the six variables, it was possible to stratify patients into low (0–1 variables), intermediate (2 variables), or high ($\geqslant$3 variables) risk groups with different 10-year survival rates (65%, 54%, and 11%, respectively; $P<0.0001$). In this study, Hb level was a prognostic factor in the univariate analysis, but in the multivariate analysis it was not established as an independent prognostic parameter.

Mantle cell lymphoma is an aggressive subtype of NHL with a high rate of relapse after initial treatment. Once relapse occurs, the disease becomes even more aggressive and more refractory to treatment and is inevitably terminal, with a median survival of 3–4 years. Two retrospective studies of mantle-cell lymphoma have considered Hb levels as one of the prognostic factors. The first study analysed 34 patients whose cancer had been reclassified as mantle cell lymphoma [12]. These patients were part of a larger group of 69 patients originally classified as Working Formulation groups B and E. The majority (30/34) had received anthracycline therapy. Median OS was 41 months for the mantle cell lymphoma group; univariate analysis showed that longer OS was associated with a nodular histological pattern ($P=0.054$), IPI score under 2 ($P=0.0027$), response to therapy ($P=0.0125$), and higher Hb levels (>12 g/dl; $P=0.02$). Notably, response to therapy, which was already a prognostic parameter by itself, was influenced only by Hb level ($P=0.054$), demonstrating that the Hb level was also a predictive factor. The second study considered the outcomes of 121 patients with mantle cell lymphoma who were treated at a French hospital between 1979 and 1997 [13]. 37% of the patients had anemia at diagnosis. In the univariate analysis, Hb levels were not associated with response to initial treatment or PFS; however, higher Hb levels (>12 g/dl) were associated with a significantly longer OS ($P=0.014$). Other factors associated with a longer survival in this analysis included age under 70 years ($P=0.0075$), good performance status ($P=0.001$), localized stage I or II disease ($P=0.02$), fewer than two

extranodal sites ($P=0.00034$), no spleen enlargement ($P=0.04$), absence of peripheral blood involvement ($P=0.0017$) and normal serum LDH and β_2-microglobulin levels ($P=0.009$ and $P=0.04$, respectively). In the multivariate analysis, only low Hb level, age >70 years, poor performance status, blood involvement and bulky disease were associated with a poorer OS.

Taken together, these studies suggest that Hb level is a prognostic factor for OS in NHL, particularly for those with an aggressive histological subtype, and is a predictive factor in mantle cell lymphoma.

2.2. Hodgkin's disease

The International Prognostic Factors Project on Advanced Hodgkin's Disease considered the prognostic value of 19 demographic and clinical variables at diagnosis on PFS [14]. Data were obtained retrospectively from 25 centers for 5141 patients who were treated with combination chemotherapy with or without radiation therapy for advanced Hodgkin's disease. 33% of patients had Hb levels of 10.1–12.0 g/dl at diagnosis and 17% had levels ⩽10.0 g/dl. Complete data for all 19 variables were available for 1681 patients. In the univariate analysis, low Hb level was inversely related to PFS and OS (both $P<0.001$). Several other variables were significantly related to both outcomes, including age, gender, Ann Arbor stage, liver or inguinal involvement, systemic symptoms, ESR, serum albumin, alkaline phosphatase and white cell, platelet and lymphocyte counts. However, using the multivariate Cox model, only seven factors had adverse prognostic significance for PFS: Hb <10.5 g/dl ($P=0.006$), serum albumin <4 g/dl ($P<0.001$), male gender ($P=0.001$), stage IV disease ($P=0.011$), age of 45 years or older ($P=0.001$), leukocytosis (white cell count $\geqslant 15\,000/mm^3$) ($P=0.001$), and lymphocytopenia $<600/mm^3$ ($P=0.002$). Using this model, PFS at 5 years was inversely related to the number of prognostic factors, ranging from 84% for those with no factors to 42% for those with five or more factors. Five-year OS rates ranged from approximately 90% for patients with no prognostic factor or only one factor to 56% for those with five or more factors.

Two other studies highlight the prognostic value of Hb levels in Hodgkin's disease. A retrospective evaluation of the medical records of 87 patients who presented at the M.D. Anderson Cancer Center with stage I or II subdiaphragmatic Hodgkin's disease found that Hb levels ⩽12 g/dl ($P=0.02$), albumin level <3.5 g/dl ($P=0.0002$), age over 40 years ($P<0.00001$), B symptoms ($P=0.001$) and nodular sclerosis or mixed cellular histology ($P=0.001$) independently predicted poorer OS in a univariate analysis [15]. On multivariate analysis, decreased Hb levels, age greater than 40 years, and nodular sclerosis or mixed cellularity histology were independent risk factors for OS. Most of the patients in this analysis had been treated with radiotherapy either alone (69%) or in combination with chemotherapy (26%), and most had pelvic or abdominal disease (64%) at presentation. Approximately 15% had Hb levels of less than 12 g/dl prior to treatment. In a pediatric study, 202 children with Hodgkin's disease received four cycles of a chemotherapy regimen devoid of anthracyclines and alkylating agents (vinblastine, bleomycin, etoposide, and prednisone) followed by 20 Gy of radiation therapy [16]. After a median follow-up of 74 months, the 5-year OS and event-free survival rates were 98% and 91%, respectively. In the multivariate analysis, Hb levels <10.5 g/dl ($P=0.003$), 'b' biologic class ($P=0.06$), and nodular sclerosis histology ($P=0.002$) predicted poorer event-free survival. These studies indicate that the Hb level holds prognostic significance in both adult and paediatric Hodgkin's disease.

2.3. Acute myeloid leukaemia

The prognostic value of Hb levels in patients with refractory and relapsed acute myeloid leukaemia (AML) was assessed in 254 patients undergoing S-HAM (sequential high-dose cytosine arabinoside and mitoxantrone) salvage chemotherapy [17]. The achievement of a second complete remission was related to Hb level ($P=0.0197$), absence of refractory disease ($P=0.0118$), duration of first complete remission ($P=0.0176$), and lowered white blood cell ($P=0.0296$) and blast <5% ($P=0.0315$) counts in the univariate analysis but was significantly associated only with the Hb level ($P=0.0457$) in the multivariate analysis. Also, in the multivariate analysis, overall survival was found to be related only to bilirubin level ($P=0.0166$). A sub group of 104 patients in whom karyotype analysis had been conducted before first-line therapy was evaluated separately. In this sub group, unfavorable chromosomal abnormalities were found to be the only factor related to OS on multivariate analysis ($P=0.036$) and no factor (including Hb) was significantly associated with achievement of complete remission in this analysis. Thus, Hb level appears to be predictive of response to salvage chemotherapy in refractory and relapsed AML, but to not have prognostic significance for OS.

Table 1 summarizes the effect of low Hb levels on OS in retrospective analyses of hematological malignancies.

3. Hemoglobin level as a prognostic and predictive factor in solid tumors

3.1. Non–small-cell lung cancer

The Southwest Oncology Group conducted a retrospective analysis of prognostic factors in 2531 patients with extensive-stage non–small-cell lung cancer

Table 1
Effect of low Hb levels on overall survival in retrospective analyses of hematologic malignancies

Ref.	Patients	*N*	Effect on OS	Other effects
[10]	Non-Hodgkin's lymphoma	1077	Yes (uni/multi)	PFS (univariate/multivariate)
[11]	Follicular lymphoma	987	Yes (univariate)	
[12]	Mantle cell lymphoma	69	Yes (univariate)	Response to therapy (univariate)
[13]	Mantle cell lymphoma	121	Yes (uni/multi)	
[14]	Hodgkin's disease	1681	Yes (univariate)	Freedom from progression (multi)
[15]	Stage I/II subdiaphragmatic Hodgkin's disease	87	Yes (uni/multi)	
[16]	Pediatric Hodgkin's disease	202	Not evaluated	Event-free survival (uni/multi)
[17]	Relapsed/refractory AML	254	No	Achievement of second remission

AML, acute myeloid leukaemia; Hb, hemaglobin; multi, multivariate analysis; OS, overall survival; PFS, progression-free survival; uni, univariate analysis.

(NSCLC) who were accrued to 14 phase II or III studies from 1974 to 1988 [18]. In the multivariate analysis of 2290 patients for whom there were complete data, the only factors significantly associated with a favorable OS were good performance status, female sex, cisplatin-based therapy (all $P < 0.00005$) and age $\geqslant 70$ years ($P = 0.02$). However, a second multivariate analysis was conducted for a sub group of 362 patients with good performance status who were enrolled in the more recent studies. In this sub group, better OS was associated with Hb levels $\geqslant 11$ g/dl ($P = 0.001$); normal serum LDH ($P = 0.002$) and calcium ($P = 0.007$); a single metastatic site ($P = 0.02$); and cisplatin-based therapy ($P = 0.05$). Moreover, a recursive partitioning and amalgamation analysis of 904 patients from recent studies found that the best survival was achieved in patients with good performance status who had Hb levels > 11 g/dl and were older than 47 years.

A prospective study was conducted to evaluate the prognostic significance of type I collagen synthesis and degradation markers in lung cancer patients [19]. The 143 study patients had been variously treated with radiation therapy with or without surgery, radiotherapy plus chemotherapy, chemotherapy alone, surgery alone or other treatment combinations. In multivariate regression analysis, Hb level ($P < 0.002$) and ESR ($P < 0.02$), in addition to other factors, were significant prognostic factors for OS when stratified with disease stage and surgery.

Two retrospective studies confirmed the importance of Hb level as a prognostic factor in inoperable NSCLC patients who underwent radiation therapy. In a study of 96 patients, most of whom had advanced NSCLC, pretreatment Hb level > 15 g/dl was a significant positive prognostic factor for survival following primary radiation therapy ($P = 0.0001$), whereas the radiation dose was not a significant prognostic factor for survival [20]. In a study of 456 patients, 30 pretreatment variables (five tumor-associated, five patient-associated, 20 initial laboratory parameters) were evaluated as prognostic factors for survival [21]. Results of univariate analysis showed that 16 of the 30 variables, including Hb level > 12.7 g/dl ($P < 0.001$), were favorable prognostic influences. Among the other factors favorably associated with survival in the univariate analysis were low disease stage (TNM stage I + II) ($P < 0.001$), Eastern Cooperative Oncology Group (ECOG) performance status 0–1 ($P < 0.001$), lactate dehydrogenase (LDH) $\leqslant 200$ U/l ($P = 0.005$), serum gamma-glutamyl transpeptidase (GGT) $\leqslant 60$ U/l ($P = 0.035$), serum albumin > 3.5 g/dl ($P = 0.016$), platelet count $\leqslant 422$/nl ($P = 0.005$) and lymphocyte count > 2.0 nl ($P = 0.026$). Subsequent multivariate analysis showed that Hb > 12.7 g/dl ($P = 0.006$), low stage of disease ($P < 0.001$), LDH $\leqslant 200$ U/l ($P = 0.035$), serum GGT $\leqslant 60$ U/l ($P = 0.032$), and lymphocyte count > 2.0/nl ($P = 0.008$) remained significant prognostic factors for survival.

3.2. Ovarian cancer

A retrospective analysis of 553 patients with histologically confirmed epithelial ovarian cancer evaluated the prognostic significance of Hb levels before surgery [22]. In this group, 26% of patients had anemia (Hb < 12 g/dl). The 5-year OS rates were 34% and 47% in those with and without anemia, respectively ($P = 0.0014$). In a univariate analysis, Hb level ($P = 0.0001$), disease stage ($P < 0.0001$), residual tumor ($P < 0.0001$), grading ($P < 0.0001$), age ($P < 0.0001$), and histological sub group ($P = 0.0016$) were found to be significantly associated with OS. On multivariate analysis, disease stage ($P < 0.0001$), residual tumor ($P < 0.0001$) and age ($P = 0.0011$) remained significant factors influencing OS, independent of each other; also, chemotherapy was shown to be a significant prognostic factor. Pretreatment Hb level was not identified as a significant independent factor in this analysis. However, in a separate analysis of a sub group of 203 patients with stage I or stage II disease, Hb level was significantly associated with OS (rates 61% versus 74% for patients with Hb levels < 12 g/dl and $\geqslant 12$ g/dl, respectively ($P = 0.037$). In multivariate analysis, Hb ($P = 0.050$) and residual tumor ($P = 0.018$) were independent prognostic factors for OS in this sub group. The authors concluded that pretreatment anemia may identify those stage I and II patients who are at increased risk of relapse.

Predictive factors associated with response to second-line treatment were evaluated in 1185 platinum-pretreated patients with ovarian cancer [23]. These patients had participated in European Organisation for Research and Treatment of Cancer (EORTC) studies of six different chemotherapeutic agents: paclitaxel, epirubicin, docetaxel, carboplatin, irinotecan and gemcitabine. Response results from the studies were obtained for four specific variables: baseline Hb (WHO grade 0 versus grade $\geqslant 1$), serous histology (Yes/No), maximum lesion size ($\leqslant 5$ versus >5 cm), and time from last treatment (<6 months versus $\geqslant 6$ months). Initial analysis showed that response to these agents was associated with normal baseline Hb levels (WHO grade 0; $P=0.003$), serous histology ($P=0.001$), tumor size $\leqslant 5$ cm ($P=0.02$) and at least 6 months therapy-free interval ($P=0.001$). A second analysis was then performed to determine if the various predictors were independent of each other. For this analysis, data for 11 variables from four studies of paclitaxel, docetaxel and epirubicin ($n=704$) were combined for univariate and multivariate analysis of factors predictive of response. Ten of the 11 factors, including baseline Hb, were considered in the regression analysis but, in the final model, only three remained as significant independent predictors of response: serous histology ($P=0.009$), number of disease sites ($P=0.003$), and tumor size ($P=0.001$). Thus, in the setting of relapsed disease, tumor burden and histology appear to be more important than Hb level in predicting response to second-line treatment of ovarian cancer.

3.3. Cervical cancer

Studies in patients with cervical cancer have also demonstrated that Hb level is a significant prognostic factor for outcome. In a retrospective analysis of data from 605 cervical cancer patients treated with radiation therapy with or without chemotherapy at seven Canadian institutions in 1989, 1990 and 1992, a baseline Hb $\geqslant 12.0$ g/dl was shown by univariate analysis to be a significant prognostic factor for higher rates of OS ($P<0.003$), local control of disease ($P=0.002$) and DFS ($P=0.005$) [24,25]. On multivariate analysis, baseline Hb was no longer a significant prognostic factor, but average weekly nadir Hb (AWNH) during radiation therapy ($P=0.0001$) and tumor stage ($P=0.0001$), intracavitary treatment ($P=0.0004$) and squamous histology ($P=0.0446$) were significant factors for outcome. Further multivariate analysis, in which outcomes were stratified by higher Hb ($\geqslant 12.0$ g/dl) versus lower Hb (<12.0 g/dl) at baseline and during radiation therapy, showed significantly higher rates of overall survival ($P<0.0002$) and lower rates of relapse ($P=0.001$), local disease recurrence ($P=0.008$), and distant disease recurrence ($P=0.02$) in the groups that achieved or maintained the higher Hb levels compared with those whose Hb decreased or remained low during treatment. The investigators concluded that amelioration of anaemia and maintenance of Hb levels above 12.0 g/dl are vital to the success of radiation therapy in cervical cancer patients.

An Australian study retrospectively examined the effect of anemia before and during chemo-irradiation in 57 patients with cervical carcinoma [26]. Mean Hb levels at presentation and mean nadir Hb levels during treatment were 12.9 and 11.1 g/dl, respectively, in patients who achieved a complete clinical response, and 12.1 and 9.8 g/dl in those with treatment failure. Consistent with the findings of the previous study, univariate analysis identified the nadir Hb level as the most predictive factor for treatment failure (relative risk 1.92; $P=0.015$), followed by disease stage (relative risk 0.51, $P=0.074$). In a multivariate analysis, the nadir Hb remained the only relevant prognostic factor predicting response to chemo-irradiation, and only patients with nadir Hb levels >11.0 g/dl throughout treatment had a $>90\%$ chance of achieving a complete clinical response. The investigators concluded that the nadir Hb level, rather than the Hb level at the time of presentation, is highly predictive of response to treatment.

3.4. Renal carcinoma

The prognostic factors for OS in advanced renal cell carcinoma were determined in a retrospective analysis of 670 patients who were treated with chemotherapy or biological response modifiers in 24 clinical trials at the Memorial Sloan-Kettering Cancer Center between 1975 and 1996 [27]. Median survival time was 10 months. Upon multivariate analysis, a low Hb level was found to be one of five pretreatment factors associated with shorter OS. The other risk factors were poor Karnofsky performance status ($<80\%$), high 'corrected' serum LDH, high serum calcium, and absence of prior nephrectomy. Median OS was inversely related to the number of these factors, ranging from 20 months in patients with no risk factors to 4 months in those with three or more risk factors.

In a study conducted in Japan, 111 patients who underwent curative resection of renal cell carcinoma were evaluated retrospectively to determine prognostic factors for 5-year survival [28]. A univariate analysis considered the prognostic significance of 19 variables. An Hb level >12 g/dl was significantly associated with higher 5-year survival rates ($P=0.0129$). Other factors significantly associated with longer survival included body temperature $<37\ ^\circ$C ($P=0.002$), ESR $\leqslant 20$ mm/h ($P=0.002$), C-reactive protein (CRP) negative ($P=0.0005$), fibrinogen $\leqslant 400$ mg/dl ($P=0.0002$), tumor size $\leqslant 5$ cm ($P=0.0389$), Robson disease stage 1 ($P=0.0001$), pathological grade 1 ($P=0.0326$), renal

capsular involvement ($P=0.0001$) and mode of tumor infiltration ($P=0.0334$). Upon multivariate analysis, CRP ($P=0.0126$) and renal capsular involvement ($P=0.049$) were the most important prognostic factors for survival for at least 5 years following curative resection.

3.5. Head and neck cancer

Considerable evidence suggests that tumor hypoxia is common in head and neck tumors and that a relationship exists between hypoxia and anemia in patients with such tumors [29]. Additionally, numerous studies have shown that tumor hypoxia and anemia adversely affect clinical outcome following radiation therapy or chemo-irradiation therapy (reviewed by Kumar 2000 [29], Vaupel 2001 [30], and Harrison 2002 [31]). Several recent studies have examined the prognostic value of Hb levels in patients with head and neck cancer undergoing chemo-irradiation therapy. In a prospective study of head and neck cancer patients treated with combined chemo-irradiation therapy and surgery, results of a univariate analysis showed that low Hb levels (<11.5 g/dl) after treatment were significantly associated with poorer OS ($P=0.0084$) [32]. Other prognostic factors for survival included tumor size ($P=0.0088$), response of primary site to radiochemotherapy ($P=0.045$) and response of lymph nodes to radiochemotherapy ($P=0.013$).

A retrospective study of 191 patients with squamous cell carcinoma of the oral cavity and oropharynx was conducted using records from an Austrian hospital for the years 1989–1998, inclusive. Patients had been treated with mitomycin, 5-fluorouracil and radiation therapy, followed by surgery [33]. Starting in 1996, patients with low Hb levels (<12.5 g/dl) before or during chemo-irradiation additionally received epoetin alfa to correct their anemia. For data analysis, patients were classified according to whether their pretreatment Hb was <14.5 g/dl and whether they had received epoetin alfa during chemo-irradiation therapy. Results of multivariate analysis showed that Hb level and the use of epoetin alfa were independent prognostic factors for response to chemo-irradiation and locoregional tumor control ($P<0.001$). Patients with pretreatment Hb levels >14.5 g/dl had significantly higher complete response, locoregional control, and OS rates than those with pretreatment Hb levels <14.5 g/dl who had not received epoetin alfa ($P<0.05$). Further, response, locoregional control and OS rates in patients with low Hb levels given epoetin alfa were significantly higher than those in patients with low Hb levels who had not received epoetin alfa ($P<0.001$), and were equivalent to those of patients with pretreatment Hb levels >14.5 g/dl ($P>0.3$). These findings suggested that low pretreatment Hb is a negative prognostic factor for patients with squamous cell carcinomas of the oral cavity and oropharynx, but that this can be reversed by administration of epoetin alfa during chemo-irradiation therapy.

3.6. Other solid tumours

In hormone-refractory prostate cancer, a Cox proportional hazard model for survival time was used to evaluate whether serial measurements of Hb level and body weight improved the prognostic significance of a model based on prostate-specific antigen (PSA) and its rate of change [34]. A total of 348 patients who participated in two Cancer and Leukemia Group B studies were evaluated. Both Hb level and body weight were significantly related to survival (both $P<0.0001$). Serial measurements of Hb levels and body weight were shown to add significant prognostic information to that provided by PSA alone.

Taken together, these results indicate that Hb level is a prognostic factor for survival in a number of solid tumors, including NSCLC and ovarian, cervical, head and neck and prostate cancers. Table 2 summarizes the effect of low Hb levels on OS in retrospective analyses of solid tumors.

4. Anemia and staging systems

Anemia is a common feature of both chronic lymphocytic leukemia (CLL) and multiple myeloma and is a component of the staging systems for both diseases. The causes of anemia in CLL are multifactorial and may include extensive bone-marrow infiltration by lymphocytes, autoimmune hemolysis, hyperspleenism, blood loss or anemia of chronic disease with associated cytokine-driven inhibition of erythropoietin production and diminished responsiveness of erythroid precursors to erythropoietin [35]. In CLL patients, Hb levels <11 g/dl designate Rai stage III disease, while levels <10 g/dl designate Binet stage C independently of lymphadenopathy or organomegaly. According to the National Cancer Institute (NCI) guidelines, chemotherapy should be considered for CLL patients with Hb levels <10 g/dl. It has been suggested that if anemia is corrected by administration of epoetin alfa, the disease may be downstaged [35]. This could affect treatment decisions, with possible postponement of chemotherapy, and perhaps even lead to improvement in survival. Such potential benefits remain to be investigated in randomized clinical trials. In multiple myeloma, anemia is often caused by inadequate production of erythropoietin [36], but it may also occur as a result of bone-marrow infiltration by malignant cells, reduced survival of red blood cells, renal insufficiency, cytokine production and the myelosuppressive effects of chemotherapy [37]. In multiple

Table 2
Effect of low Hb levels on overall survival in retrospective analyses of solid tumors

Ref.	Patients	*N*	Effect on OS	Other effects
[18]	Extensive-stage NSCLC	2531	Yes (univariate)	OS in subgroup with good PFS (multi)
[19]	Lung cancer	143	No	OS when stratified with disease stage and surgery (multi)
[20]	Inoperable NSCLC	96	Yes (univariate)	OS in subgroup with stage I/II disease
[21]	Inoperable NSCLC	456	Yes (uni/multi)	
[22]	Ovarian cancer	553	Yes (univariate)	OS in subgroup with stage I/II (multi)
[23]	Second/third-line treatment in platinum-treated ovarian cancer	1185	Not evaluated	Response to therapy (univariate)
[24]	Cervical cancer	605	Yes (univariate)	OS for average weekly nadir Hb (multivariate)
[26]	Cervical carcinoma	57	Not evaluated	Nadir Hb predictive for treatment failure (uni/multi)
[27]	Advanced renal cell carcinoma	670	Yes (multivariate)	
[28]	Curatively resected renal cancer	111	Yes (univariate)	
[32]	Advanced head and neck cancer	43	Yes (univariate)	
[33]	Head and neck cancer	191	Not evaluated	Prognostic for response to chemoradiation and locoregional control (multivariate)
[34]	HR prostate cancer	348	Yes (multivariate)	

AML, acute myeloid leukemia; Hb, hemoglobin; HR, hormone refractory; multi, multivariate analysis; NSCLC, non–small-cell lung cancer; OS, overall survival; PFS, progression-free survival; uni, univariate analysis.

myeloma patients, an Hb level >10 g/dl is a determining factor for stage I disease and Hb <8.5 is a determining factor for stage III [38]. In most patients, anemia improves when the disease responds to chemotherapy [39]. However, if this does not occur, or chemotherapy is not required, the anemia may be treated with blood transfusions or, given the inherent risks of the latter, administration of epoetin alfa [39]. A small proportion of patients, e.g. those with smouldering multiple myeloma, have asymptomatic disease and do not require chemotherapy. However, these patients often develop anemia serious enough to require intervention and may subsequently be given chemotherapy to address the anemia. In such cases, epoetin alfa should be considered as a possibility for avoiding, at least temporarily, initiation of chemotherapy.

5. Preclinical evidence

Several experimental studies provide evidence supporting the prognostic significance of Hb level. In the rat 9L gliosarcoma model, administration of an Hb solution reduced the level of tumor hypoxia [40]. The response of the tumor to chemotherapy and radiation therapy was assessed by determining the tumor growth delay under conditions of anti-angiogenic therapy with TNP-470 and minocycline alone or in combination with an Hb solution with or without carbogen breathing. Tumor response was strongly correlated with decreasing tumor hypoxia. Specifically, tumor growth delay due to carmustine (BCNU), doxorubicin or fractionated radiation therapy was enhanced when these agents were administered in combination with TNP-470 and minocycline, and this effect was further enhanced by the addition of Hb solution with or without carbogen breathing to the individual combinations. For example, tumor growth delays were 4.8 days with radiation therapy alone, 5.8 days with radiation plus TNP-470/minocycline, 10.8 days with radiation plus TNP-470/minocycline and the Hb solution and 13.3 days with the previous combination plus carbogen breathing. Comparable values for BCNU with treatment-related increases in oxygenation were 5.3, 9.9, 10.4 and 16.4 days. These data highlight the fact that addition of oxygenation-enhancing agents to radiation therapy or some chemotherapeutic agents can improve therapeutic response.

Similar results were obtained with polyethyleneglycol (PEG) hemoglobin in the rat 13762 and murine EMT-6 mammary carcinoma models [41]. Polyethyleneglycol hemoglobin reduced tumor hypoxia before and after administration of chemotherapy. Moreover, PEG hemoglobin increased the tumour growth delay produced in these models by cyclophosphamide, doxorubicin, 5-fluorouracil, BCNU and paclitaxel. This benefit of PEG hemoglobin was associated with a concomitant reduction in lung metastases. The results of the preclinical studies described suggest that increasing tumor oxygenation may markedly enhance the therapeutic response to cytotoxic chemotherapy and radiation therapy in these models.

Another strategy for increasing Hb level is to administer epoetin alfa. The effect of epoetin alfa on the antitumor activity of cisplatin was evaluated in female severe-combined immunodeficient (SCID) mice with human ovarian cancer xenografts [42]. One group of mice had large ovarian cancer xenografts implanted on the gonadal fat pad, whereas another group of SCID mice had small subcutaneous ovarian cancer xenografts. Animals in each group were given one of four treatments: epoetin alfa 20 units three times per week,

cisplatin 5 mg/kg weekly, epoetin alfa plus cisplatin, or phosphate-buffered saline control.

The growth of the large tumors was significantly delayed by cisplatin with or without epoetin alfa compared with the control group ($P < 0.05$). In these animals, the addition of epoetin alfa did not significantly affect the growth delay relative to cisplatin alone ($P = 0.07$). In contrast, significantly greater tumor regression was achieved with combined cisplatin plus epoetin alfa compared with cisplatin alone in the SCID mice with small subcutaneous tumors ($P < 0.05$). Epoetin alfa alone did not have any antitumor activity. The benefit of epoetin alfa was associated with a 25–35% increase in hematocrit, which differed significantly from the 2% decrease seen with saline control ($P < 0.01$). In comparison, the animals that received cisplatin displayed a 20% reduction in hematocrit. Epoetin alfa reduced the morbidity associated with cisplatin therapy when performance status scores based on five objective criteria associated with morbidity and mortality in experimental mice (ruffled fur, weakness/lethargy, weight loss, kyphotic hunched posturing and death) were assessed after the first (26 versus 17 points) and second (43 versus 29 points) weeks of therapy. These results demonstrate that epoetin alfa improves responsiveness of human ovarian cancer xenografts to cisplatin, which is associated with an increase in hematocrit and reduction in morbidity.

6. Conclusion

Clinical evidence shows that Hb level is a prognostic factor for OS and/or DFS in several hematological malignancies and solid tumors. Hemoglobin level is also a negative predictive factor for response to treatment, in particular to chemotherapy in AML and mantle cell lymphoma, and possibly in relapsing ovarian cancer. This body of clinical evidence is supported by experimental data in animal tumor models. Nevertheless, it is important to recognize that the available clinical evidence is based almost exclusively on retrospective analyses of medical records. This underscores the need for prospective clinical trials that are designed specifically to ascertain whether Hb levels affect treatment outcome. In a 28-week multinational study designed to explore the efficacy of epoetin alfa on anemia and QOL in anemic cancer patients receiving non-platinum-based chemotherapy, a trend was observed suggesting that epoetin alfa may improve survival [43]. Randomized trials designed to confirm a survival benefit of epoetin alfa are clearly needed. In conclusion, there is more than one reason to pay attention to Hb levels in cancer patients: not only is normalizing Hb important for improving QOL, but it may also play a role in influencing outcome.

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