The prognostic value of hemoglobin level in cervical cancer patients

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Abstract

The present paper aim to assess the prognostic value of pretreatment hemoglobin (Hb) level in cervical cancer patients. A number of 142 adenocarcinoma (AC) and 242 squamous cell cancer (SCC) patients, FIGO stage I-IVA, treated with surgery and radiotherapy (RT) or RT alone, were analyzed retrospectively. Factors as the pretreatment Hb level, FIGO stage, the tumor diameter, the histopathology, and WHO status were analyzed. As the cut-off value of Hb level, 10 g/dl and 13 g/dl was accepted. Independently of the other factors, the pretreatment Hb level in cervical SCC patients had statistically significant association with overall survival (OS) (p=0.031) and disease free survival (DFS) (p=0.019). In patients with AC, Hb level was not statistically significant for OS (p=0.58) and DFS (p=0.29). The pretreatment Hb concentration in patients with SCC of the uterine cervix seems to be an important prognostic factor.
Keywords: *cervical cancer, hemoglobin level, prognostic factors, treatment results*

Introduction

Cervical cancer is the fifth cause of death and the second cause of malignant morbidity among women. The most frequent sign of the disease is acute or chronic bleeding and malnutrition, what consequently causes the anemia in a significant percentage of cervical cancer patients. The relationship between anemia and poor outcomes of radiotherapy (RT) or radiochemotherapy (RCT), the standard treatment method of advanced cervical cancer patients, is the subject of a few publications[1-4]. The aim of the study was to examine the prognostic significance of pretreatment hemoglobin (Hb) level in cervical cancer patients[5].

Methods

The clinical material constituted 142 cervical adenocarcinoma (AC) and 242 squamous cell cancer (SCC) cervical cancer patients, with International Federation of Gyneacology and Obstetrics (FIGO) stage I-IVA treated at Maria Sklodowska - Curie Memorial Cancer Center in Warsaw between January 1989 and December 1999. In 2000 the treatment of cervical cancer patients with RCT was started. All patients were treated with surgery and complementary radiotherapy (RT) or RT alone. For all cases, cancer was confirmed histologically. Informed consent was obtained before the treatment from all subjects, according to the World Medical Association Declaration of Helsinki. A total of 384 patients accepted for radical treatment, were included in the statistical analysis.

Initial loco - regional staging involved clinical examination, as well as abdominal and pelvic computed tomography. Cystoscopy or rectoscopy with biopsy confirmation was performed on patients presenting suspected infiltration of the bladder or rectum. Chest radiogram and blood chemistry were assessed.

Patients with risk factors in post surgical histological protocol were treated with external beam radiotherapy (EBRT) with brachytherapy (BT) or BT alone with Cesium (Cs) -137, and Iridium (Ir)-192. The 4-field treatment technique was performed. The target in 2D planning for EBRT was defined by bony landmarks and calculated with Mevaplan system, according to the International Committee on Radiation Units and Measurements (IRCU) 50 and ICRU 62 protocol and was treated with high megavoltage photons from a linear accelerator (X 6, 9 and 15 Megaelectron volts) or Cobalt-60 (Co-60). EBRT was administered in daily fractions of 1.8-2 Gy, amounting to total doses of up to 45-50 Gy to the elective area and approximately 60 Gy to enlarged lymph nodes. The standard dose for most of the patients was 46 Gy in 23 daily fractions, 2 Gy per fraction. BT was planned in 2D, according to the ICRU 38 Report. High dose rate in fractions of 7.5 Gy and low dose rate in fractions about 20 Gy were prescribed to point-A for inoperable patients or to the upper 1/3 part of vagina for operated patients, all plans in 2D.

Follow-up examinations were scheduled every 3 months during the first 2 years and every 6 months throughout the next 3 years. In case of suspected relapse, biopsies were obtained.

Statistical Analysis

The multivariate Cox's analysis in aspect of overall survival (OS) and dosage free survival (DFS) was performed. The subjects of analysis were: the FIGO stage, age, the pretreatment tumor diameter, the histological type of the tumor, WHO status, and the pretreatment Hb level. Based on the studies and recommendations as the cut-off value of Hb level, 10 and 13 g/dl were accepted. P-values ≤0.05 were considered statistically significant.

Results

The median age of patients was 54 years (range 25-85), and the median follow-up time for the living patients was 52 months (range 9-174).

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FIGO stage I had 111 (29%), II – 132 (34%), III – 130 (34%) and IV – 11 (3%) of patients. Mean Hb level was 12.1 mg/ml (range 4.1-16). Most of the patients (92%) had WHO performance status 0-1. The percentage of well and moderately differentiated histological features was 60. Most of the patients (57%) had a tumor diameter over 3 cm. Surgery was performed on 53 % of the patients with AC and 23% with SCC. About 53.5% had Wertheim-Meigs radical hysterectomy (RH) surgery and 46.5% had hysterectomy. EBRT was performed on 340 (88.5%) patients, BT alone or combined with EBRT on 257 (70%).

In multivariate analysis, independently of the other clinical and histological factors, pretreatment Hb level (≥13 vs <13) in SCC patients had statistically significant association with OS, hazard ratio (HR) 0.6, CI 95% = 0.38 - 0.95, p=0.031), and DFS (HR=0.6, CI 95% =0.4 - 0.92, p=0,019) (Figure 1, 2). In patients with AC, Hb level (≥13 vs <13) did not demonstrate a statistically significant impact on OS (p=0.58) and DFS (p=0.29). Hb level 10 mg/ml had an impact on DFS (0.004) in SCC patients only, with no impact on OS (p=0.2).

Discussion

CCR combined with BT is the standard radical treatment for advanced stage cervical cancer. The weakness of our study is the retrospective character of analysis and lack of chemotherapy used in that time. But study cohort is large and all patients were treated according to the same protocol. Data on the SC cervical cancer patients comes from the shorter term to achieve a comparable group in number with AC patients. Results of studies regarding the value of Hb level as prognostic factor are inconclusive[2]. The levels of pretreatment Hb were analyzed: 10 mg/ml and 13 mg/ml. The higher level proved prognostic value for OS and DFS, but only in SCC patients. The lower Hb level had limited value. Interesting is the fact that there was no impact of Hb level on survival in AC patients. This observation emphasizes different biology of the AC histological type. Contrary, in recent data published by Huang et al. concerning patients with AC, low Hb level (<10 mg/ml) remained a significant factor for predicting local relapse and total relapse events[5]. The prognostic value of Hg in surgically treated cervical cancer patients for OS was recently documented by Demirci et al.[6]. Gaducci et al. drew opposite conclusions concerning patients with locally advanced cervical cancer treated with neoadjuvant chemotherapy and RH[7].

Hypoxic cells are radioresistant. Most cervical cancer patients in our country are in the advanced stage of disease and are treated by CCR combined with BT. Secondary anemia is a popular problem. Some authors suggest transfusing blood before RT to patients with Hb level below 10 mg/ml[4]. Unfortunately, transfusions to the Hb level of about 10 mg/ml can improve general condition, but not OS[1]. Additionally, the value of blood transfusion is controversial because of immunosupression.

Another method of improving Hb level is the use of erythropoesis-stimulating agents[8,9]. Unfortunately, recently published metaanalysis reported by Bennet et al. proved

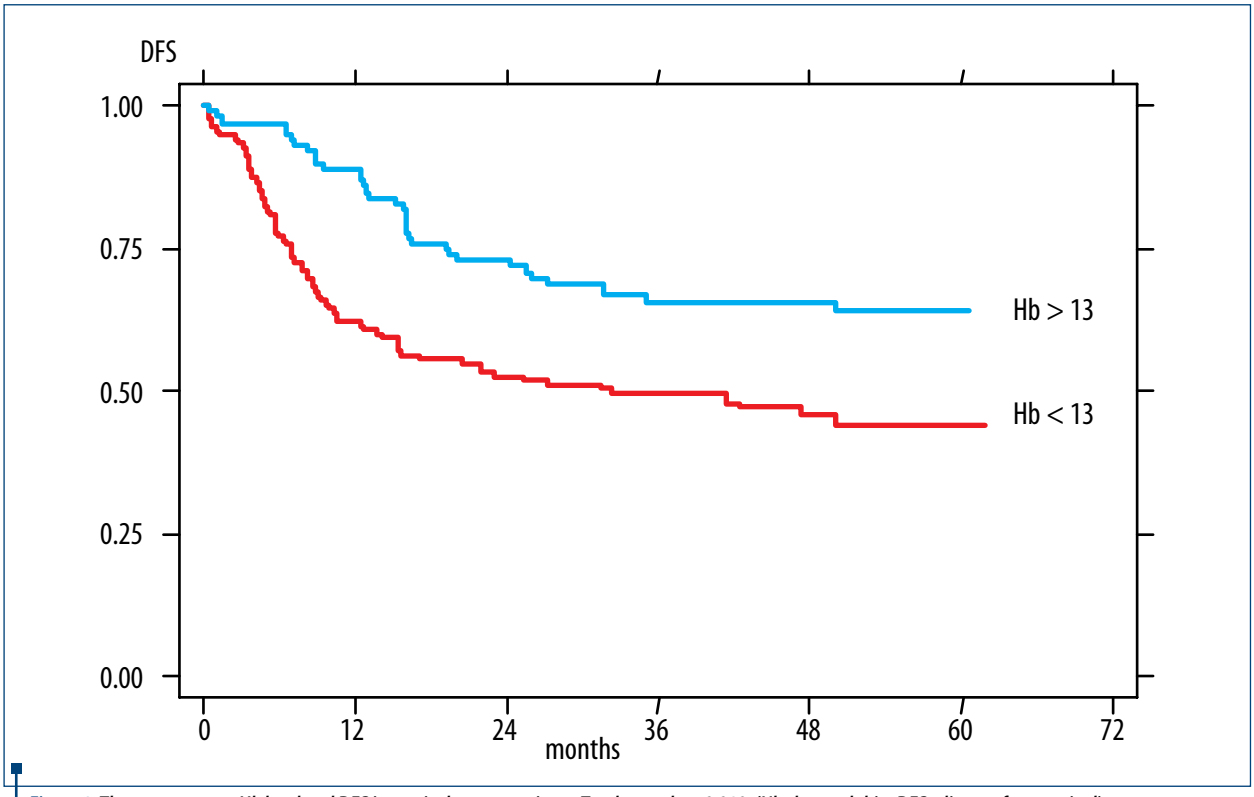

Figure 1. The pretreatment Hb level and DFS in cervical cancer patients. Test log rank p=0.019, (Hb=hemoglobin, DFS=disease-free survival)

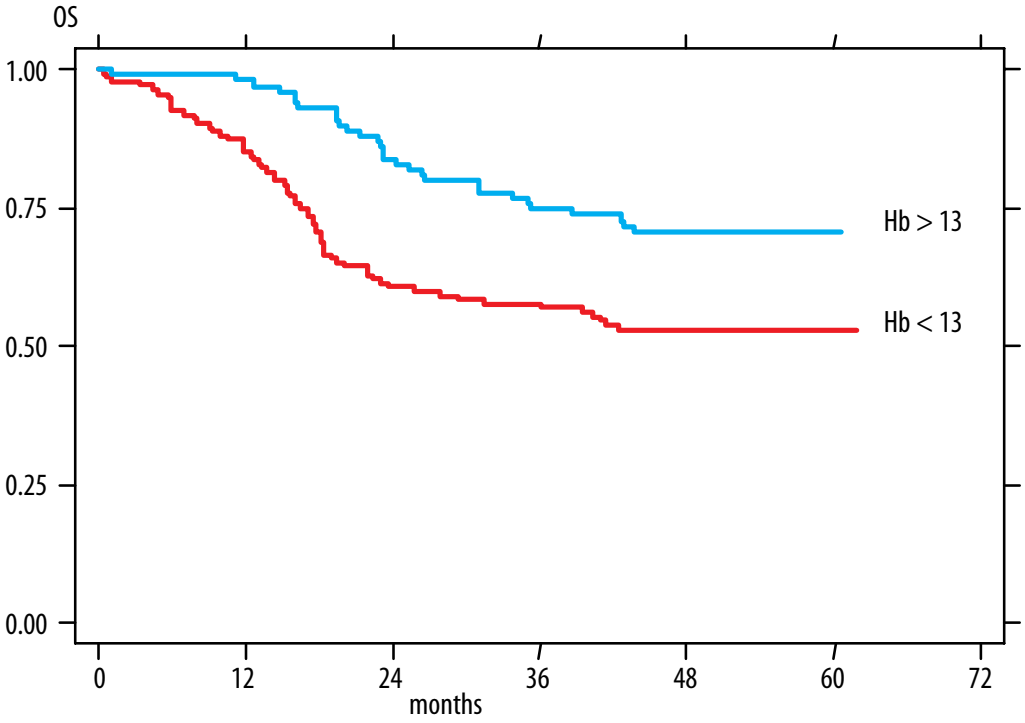

Figure 2. The pretreatment Hb level and OS in cervical cancer patients. Test log rank p=0.031, (Hb=hemoglobin, OS=overall survival)

that erythropoiesis-stimulating agents (ESAs) administration to patients with cancer was associated with increased risk of venous thromboembolism and mortality[10]. Cervical cancer cells constitutively express erythropoietin and erythropoietin receptor, therefore ESAs can inhibit apoptosis, influence proliferation and migration of tumor cells[11,12].

Another interesting study published aimed to investigate the relationship between Hb levels, corpus invasion and nodal metastases, two features not contained in FIGO stage, as to which is the strongest prognostic factor[13]. They found that pretreatment anemia (Hb<12 mg/ml) was not an independent prognostic factor. But patients with low pretreatment Hb level and low nadir which tend to have more corpus invasion and nodal metastases. The authors set the hypothesis that this nadir is associated with bone marrow reserve. Low reserve causes more infiltrating tumor growth. Subclinical chronic hypoxemia results in a more invasive and metastatic disease. Correction of anemia during treatment should improve local control without the effects of metastases and survival. Observation of Hb level before and during treatment as a biological marker of cancer aggressiveness is worth the prospective research. This hypothesis may explain the complexity of the problem and the conflicting results of published studies to date.

Conclusions

The pretreatment Hb concentration in cervical cancer patients seems to be an important prognostic factor. ■

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