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Original Research Article

Anemia, leukocytosis and thrombocytosis as prognostic factors in patients with cervical cancer treated with radical chemoradiotherapy: A retrospective cohort study

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ABSTRACT

Introduction: Anemia has long been associated with poor prognosis in patients with cervical cancer. Recently, additional hematologic parameters have emerged as potential indicators of worse outcome in this patient group. In a cohort of cervical cancer patients treated with chemoradiotherapy (CRT) and brachytherapy, we report on the prognostic significance of hematologic parameters including anemia, leukocytosis, neutrophil to lymphocyte ratio (NLR), and thrombocytosis, the effect of combining anemia with other hematologic parameters, and the effect of changes in hemoglobin levels during treatment.
Materials and methods: Two-hundred fifty-seven cervical cancer patients were retrospectively identified from a single cancer institution's database. Hematologic parameters were categorized as: anemia (hemoglobin $\leq$115 g/L), leukocytosis (white blood cell count >10 $\times$ 10^9/L), thrombocytosis (platelets >400 $\times$ 10^9/L), and NLR (ratio >5). The association between clinical factors and hematologic parameters on progression-free survival (PFS) and overall survival (OS) were assessed at 5 years.
Results: At 5 years, both pre-treatment anemia (PFS: 60% vs 34%, $p < 0.0001$; OS: 68% vs 41%, $p < 0.0001$) and on-treatment anemia (PFS: 62% vs 40%, $p < 0.0001$; OS: 70% vs 48%, $p < 0.0001$) were significantly associated with worse survival. This adverse effect on 5-year PFS and OS was increased in patients with both pre-treatment anemia and leukocytosis (PFS: 72% vs 42%, $p < 0.0001$; OS: 68% vs 37%, $p < 0.0001$) and pre-treatment anemia and elevated NLR (PFS: 61% vs 30%, $p < 0.0001$; OS: 68% vs 37%, $p < 0.0001$). Five-year PFS (50% vs 31%) and OS (60% vs 36%) was better in patients whose pre-treatment anemia improved to normal hemoglobin levels on treatment vs those patients who were anemic both pre- and on-treatment.
Conclusion: Pre-treatment and on-treatment anemia were significant, independent predictors of worse PFS and OS. Anemia and other hematologic parameters remain prognostic markers for cervical cancer patients. Improvement in PFS and OS was seen in patients with normalization of hemoglobin.

Introduction

Cervical cancer remains a significant worldwide health challenge and many patients die from the disease. Clinically meaningful prognostic markers to inform clinical practice are needed. In addition to advanced tumour stage, anemia has been described as a poor prognostic factor in cervical cancer patients [1–6]; however, the mechanism is poorly understood and several hypotheses have been explored, including tumour hypoxia, tumour size, and the impact of transfusion [1–7].

Abbreviations: Hgb, hemoglobin; NLR, neutrophil-to-lymphocyte ratio; CRT, chemoradiotherapy; EBRT, external beam radiotherapy; BT, brachytherapy; WBC, white blood cell; Plt, platelet; PFS, progression free survival; OS, overall survival; AOTHgb, average on treatment hemoglobin; LDR, low dose rate; HDR, high dose rate; PA, paraortic; PTHgb, pre-treatment hemoglobin.

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Most reports concur that anemia in cervical cancer patients portends a worse prognosis; however, there is disagreement as to whether pre-treatment or on-treatment hemoglobin (Hgb) is most prognostic [1–4,6]. The use of transfusion and other means of improving Hgb levels have been investigated and results are also conflicting [1–4,6]. Recently, a review of cervical cancer patients, with various FIGO stages and treatments, has challenged the notion of anemia being a poor prognostic marker [8].

In addition to anemia, other hematologic parameters have been investigated; most notably is tumour related leukocytosis as a poor prognostic marker in several cancers including anal canal [9] and cervical [5,10–15]. Others have reported on more general hematologic markers and markers of inflammation such as neutrophilia [15] and elevated neutrophil-to-lymphocyte ratio (NLR) [10,11,14].

In this study, we report on hematologic parameters (anemia, leukocytosis, thrombocytosis and NLR) and their prognostic significance in cervical cancer patients treated with radical chemoradiotherapy (CRT). Additionally, we evaluated the prognostic significance of Hgb levels pre- and on-treatment. This is the first study to comprehensively evaluate these hematologic factors in this patient population.

Materials and methods

Patients and treatment

With ethics board approval, patients treated with curative intent CRT between 1998 and 2012 were identified through a retrospective review of a single institution's cervical cancer patient clinicopathologic database. All patients had histologically confirmed cervical cancer and were staged according to FIGO criteria. Pre-treatment investigations included physical examination, imaging, and bloodwork. Patients were treated with external beam radiation (EBRT) to the pelvis (45 Gy in 25 daily fractions over 5 weeks) ±extended field to cover part of the paraortic (PA) nodes or the full PA nodes, with concurrent weekly cisplatin-based chemotherapy at 40 mg/m^2 for all patients. Brachytherapy (BT) was administered according to institution practice. Low dose rate (LDR) BT at 20 Gy × 2 fractions over 2 weeks was used up to late 2006 and high dose rate (HDR) BT at either 6.5 Gy × 4 fractions or 8 Gy × 3 fractions weekly to present. BT was prescribed to Point A as per ICRU 38 [16]. Patients had weekly bloodwork during CRT, and institution guidelines recommended transfusion to maintain hemoglobin >100 × 10^9 g/L. No patients were treated with erythopoietin. Patients were followed every 3–4 months for the first 2 years, then every 6 months up to 5 years, then discharged back to their community physicians.

Diagnostic definition of hematologic parameters

Leukocytosis was defined as a white blood cell (WBC) count >10 × 10^9/L [12]. Patients with a documented infection or pre-existing hematologic disorder were excluded from analysis. Anemia was defined as Hgb ≤115 × 10^{9}g/L [5], thrombocytosis was defined as platelet (Plt) count >400 × 10^9/L, and NLR was calculated as the absolute number of neutrophils/lymphocytes, and a ratio greater than 5 was considered elevated [10]. All pre-treatment hematologic parameters were evaluated from the same blood sample taken at the time of diagnosis, prior to any interventions (including transfusions or CRT). On-treatment Hgb and WBC measurements were recorded and calculated as the mean on-treatment value.

Statistical analysis

Baseline patient, tumour and treatment characteristics were evaluated with descriptive statistics using Wilcoxon's rank sum, Pearson's χ^2 test and Fisher's exact tests where appropriate. Progression-free survival (PFS) and overall survival (OS) were assessed at 5-years and were measured from date CRT was completed and date of diagnosis respectively. Overall follow-up was measured from date of diagnosis to last known date alive, as interpreted through retrospective chart review. The log-rank test was utilized for comparisons between groups of interest visualized with Kaplan–Meier graphs. Clinically relevant variables were included in multivariate analysis and backwards approach was used to establish final Cox proportional hazard regression models. Lymph node status was determined as negative or positive, for pelvic and/or PA nodes, based on diagnostic CT imaging. All p-values reported were 2-sided, and $p < 0.05$ was considered to be statistically significant. Statistical analyses were performed using Stata version 12.0.

Results

Patient and treatment characteristics

Patient, tumour, and treatment characteristics are summarized in Table 1. Two hundred-fifty-seven patients were included. Forty-five percent ($n = 116$) of tumours were FIGO stage II and 87% ($n = 222$) were squamous cell carcinomas. Ninety-eight percent ($n = 252$) of patients received brachytherapy in addition to pelvic EBRT, 5.8% ($n = 15$) were treated with full pelvic and PA node radiation technique, and 94.6% ($n = 243$) received 3 or more cycles of concurrent cisplatin-based chemotherapy. Fifty-eight (22.6%) patients had documented transfusions as part of their treatment course.

For the entire cohort, median follow-up was 40.8 months (range 4.4–167.1), median PFS was 31 months (range 0.5–163) and median OS was 40 months (range 4–167). 5-year PFS and OS was 52% and 60% respectively. On univariate analysis, worse PFS and OS was associated with larger tumour size (>5 cm), [HR 1.73 (95% CI 1.17–2.56), $p = 0.006$] and [HR 1.70 (95% CI 1.09–2.64), $p = 0.019$], respectively, and FIGO stage (I-II vs III-IV) [HR 1.9 (95% CI 1.33–2.80), $p = 0.001$] and [HR 2.00 (95% CI 1.32–3.03), $p = 0.001$]. Result details for the univariate analysis for all clinical variables can be found in Supp. Table 1.

Hemoglobin level

Anemia was documented in 28.8% ($n = 74$) of patients. Median pre-treatment Hgb (PTHgb) was 128 g/L (Table 2). On univariate analysis, pre-treatment anemia was associated with worse 5-year PFS and OS: 60% vs 34%, [HR 2.4 (95% CI 1.67–3.56), $p < 0.001$] and 68% vs 41%, [HR 2.49 (95% CI 1.64–3.81), $p < 0.001$] respectively. This association remained significant on multivariate analysis: 5-year PFS [HR 2.0 (95% CI 1.38–2.97), $p < 0.001$] and OS [HR 2.76 (95% CI 1.79–4.25), $p < 0.001$]. Median average on-treatment hemoglobin (AOTHgb) was 118 g/L (Table 2). AOTHgb levels were also significantly associated with worse 5-year PFS and OS on univariate analysis: 62% vs 40%, [HR 2.24 (95% CI 1.54–3.26), $p < 0.001$] and 70% vs 48%, [HR 2.44 (95% CI 1.60–3.73), $p < 0.001$] respectively. On multivariate analysis, AOTHgb was independently associated with outcome: 5-year PFS [HR 2.02 (95% CI 1.38–2.97), $p < 0.001$] and OS [HR 2.18 (95% CI 1.41–3.36), $p < 0.001$]. Detailed results for multivariate analysis can be found in Supp. Table 2.

Leukocytosis and NLR

Leukocytosis was documented in 26.9% ($n = 69$) of patients, and an elevated NLR in 20.2% ($n = 52$) of patients (Table 2). On univariate analysis, pre-treatment leukocytosis had worse 5-year OS 63%