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Original Article

Pre-treatment Haemoglobin and Peripheral Blood Lymphocyte Count as Independent Predictors of Outcome in Carcinoma of Cervix

P.J. Hoskin, A.M. Rojas, S.N. Peiris, V. Mullassery, I.Y. Chong

Cancer Centre, Mount Vernon Hospital, Northwood, Middlesex, UK

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Abstract

Aims: To evaluate pre-treatment haemoglobin and peripheral blood lymphocyte (PBL) counts as predictors of treatment outcome in cervix carcinoma treated with radical chemoradiation.

Materials and methods: Pre-treatment PBL counts and haemoglobin concentrations were retrieved from full blood count examinations from 111 patients who received concurrent chemoradiotherapy. Overall survival and relapse-free survival were obtained using the Kaplan–Meier method by ranking the data by median haemoglobin and PBL, singly and then in association. Their independence and significance as predictors of outcome were analysed using the Cox proportional hazard model.

Results: Survival rates were significantly higher in patients whose haemoglobin level or PBL counts were at or above the corresponding median value. At 5 years, rates of overall survival were 77% versus 41% ($P = 0.0003$) and 75% versus 42% ($P = 0.002$), when dichotomised around median haemoglobin and PBL, respectively. In multivariate and univariate analyses, both PBL and haemoglobin were independent and significant predictors for risk of death and relapse. Their predictive power was dramatically enhanced when the data were stratified into four groups by associating patients with haemoglobin $\geq$ median or $<$ median with those whose PBL was $\geq$ or $<$ median.

Conclusion: Baseline PBL and haemoglobin seem to be strong, independent predictors of treatment outcome in carcinoma of the cervix, particularly if patient response is ranked using the predictors simultaneously. The hypothesis needs to be tested and, if confirmed, the markers should be used in combination to identify those at greater risk of failure who may benefit from additional therapy, with further validation in prospective trials offering treatment modification.

Key words: Cervix cancer; haemoglobin; lymphocyte count; outcome; prognostic biomarkers

Introduction

Cervix carcinoma is a common malignancy associated with a high death rate, particularly in the developing world [1]. Concurrent chemoradiotherapy is the mainstay of treatment for patients with locally advanced disease. Despite improvements in survival and tumour control there are considerable variations in the response to treatment. There is therefore a need to identify patients at risk of failure using predictors that could influence the choice of treatment or suggest targets for the manipulation of treatment. Haemoglobin has been shown to be an independent predictor of treatment outcome in several tumour sites, among them carcinoma of the cervix (for reviews see [2,3]).

In cervix pre-treatment, haemoglobin is a strong predictor of survival [3], although some studies show haemoglobin during treatment and not pre-treatment as the independent predictor [4–6]. Other studies have shown a correlation between intrinsic measures of radiosensitivity [7], oxygen tension (see review [8]) and outcome in cancer of the cervix.

Host immunological factors have also been implicated to have an impact on treatment response and prognosis. For over four decades, peripheral blood lymphocyte (PBL) count and lymphocyte subsets have been shown to be independent predictors of survival and tumour progression in a variety of cancers [9–21]. In addition, pre-treatment lymphopenia has been identified as a risk factor for febrile neutropenia and early death in a series of pathological conditions [22–25].

We therefore retrospectively assessed survival and local regional tumour control in patients with locally advanced cervix carcinoma after concurrent chemoradiotherapy as a

Author for correspondence: A.M. Rojas, Cancer Centre, Mount Vernon Hospital, Northwood, Middlesex HA6 2RN, UK. Tel: +44-1923-829631; Fax: +44-1923-844167.

E-mail address: arc03@btconnect.com (A.M. Rojas).

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function of pre-treatment haemoglobin concentration and pre-treatment PBL count separately. We then studied whether dividing the population into four distinct categories by combining the four subsets defined by haemoglobin and PBL identifies those at 'intermediate' risk of failure and therefore a manipulation of the adverse feature would be indicated, and those at 'high risk' of failure for whom a totally different treatment management is indicated.

Materials and Methods

Clinical and laboratory data were retrospectively collected from 111 biopsy-proven cervical carcinoma patients treated at this centre between August 1999 and November 2010. Informed consent was obtained from patients before treatment.

All patients had localised carcinoma of the cervix, stage IB–IVa based on staging with pelvic magnetic resonance and chest, abdomen and pelvic computed tomography. A standard treatment of external beam radiotherapy delivered 50 Gy in 25 fractions over 5 weeks combined with five cycles of cisplatin (40 mg/m^2 per week). Upon completion of concurrent chemoradiotherapy, intracavitary high dose rate brachytherapy was administered to total doses of 14–24 Gy in two to four fractions, depending on disease stage, residual disease and tolerances of risk organs. All but one patient was treated within the stipulated standard treatment time of ≤46 days. After the completion of treatment, these patients were followed up at regular intervals and survival data updated for the current study.

A full blood count, including haemoglobin, white cell and differential count, and a biochemistry profile were carried out before administering each cycle of chemotherapy. Dose adjustments, omissions and delays were implemented as per the standard intravenous cisplatin administration protocol of this institute. Our emphasis was focused on week 1 (i.e. pre-treatment) lymphocyte count and haemoglobin level.

Statistical Analysis and End Points

Statistical comparisons were carried out using JMP™ (SAS Institute, Cary, NC, USA). Differences in patients' baseline demographics and tumour features were compared using chi-squared and Kruskal–Wallis tests for categorical and continuous covariates, respectively. Locoregional relapse, for patients who achieved complete remission, was taken as the time to local or regional recurrence or death. Time was set to zero for those with persistent tumour after treatment and for those dying within 9 months with uncontrolled primary or regional disease. Patients free of disease were censored at the time last seen. Overall survival was taken as the time to death; live patients were censored at the time of last follow-up. Both end points were measured from the date of first external beam radiotherapy dose and analyses carried out on an intention-to-treat basis. Survival rates were obtained using the Kaplan–Meier method after stratifying by median lymphocyte count or median haemoglobin level. Differences in overall survival and relapse-free survival between groups were compared using the Mantel–Cox Log-rank test. Univariate and multivariate hazard ratios were obtained using Cox's proportional hazard model with the patient and tumour features summarised in Table 1 as

Table 1
Demographic and prognostic features ranked by pre-treatment median haemoglobin concentration and median lymphocyte cell count

Variable	Category	Haemoglobin < median	Haemoglobin ≥ median	*P*	PBL < median	PBL ≥ median	*P*
Age (years)	Median	49	52	0.9	53	49	0.6
	Mean	53	53		56	50	
	Range	23–89	26–82		26–89	23–80	
FIGO stage	Ib–IIa	17% (9)	31% (18)	0.1	27% (14)	22% (13)	0.4
	IIb	53% (28)	53% (31)		46% (24)	59% (34)	
	IIIa–IVa	30% (16)	16% (9)		27% (14)	19% (11)	
Lymphocytes $\times 10^9$/l	Median	1.56	1.6	0.6			
	Mean	1.65	1.74				
	Range	0.7–3.1	0.3–3.98				
Haemoglobin g/dl	Median				12.3	13	0.1
	Mean				12.3	12.7	
	Range				8.7–16.1	9.3–16	
HDR-BT total dose	14 Gy	53% (28)	40% (23)	0.5	48% (25)	45% (26)	0.4
	18 Gy	23% (12)	24% (14)		21% (11)	24% (14)	
	21 Gy	15% (8)	21% (12)		13% (7)	22% (13)	
	24 Gy	9% (5)	15% (9)		17% (9)	9% (5)	
Cisplatin total dose (mg/m^2)	Median	180	200	0.2	160	200	0.1
	Mean	163	175		164	174	
	Range	60–200	90–200		60–200	80–200	

PBL, peripheral blood lymphocytes; FIGO, International Federation of Gynecology and Obstetrics; HDR-BT, high dose rate brachytherapy.
$P < 0.005$ considered significant.
Numbers are in parentheses.