RESEARCH ARTICLE

Haemoglobin level as the prognostic factor for patients with carcinoma of the cervix receiving radiation therapy

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Objective. The primary objective was to assess the influence of the pre-treatment and mid-treatment haemoglobin (Hb) level on local control and pelvic disease-free and overall disease-free survival in patients with carcinoma of the cervix receiving radiation therapy.

Material and methods. Seventy-two patients referred for radiation therapy for carcinoma of the cervix between January and December 2002 were entered into this prospective study. Forty-three patients (60%) had stage II and 29 (40%) stage III disease. Hb levels were checked before starting treatment and in the middle of treatment. The mean Hb levels at the start and mid-treatment were 12.8 g/dl and 12.1 g/dl, respectively.

Results. Treatment failed in 13 patients (pelvic disease 9, distant 3 and pelvic and distant 1). Patients with mid-treatment Hb levels ≥12 g/dl had significantly lower rates of pelvic failure (p=0.05) as well as overall failure (p=0.03) than patients with levels <12 g/dl. The patients with mid-treatment Hb levels ≥12 g/dl had 5-year pelvic disease-free survival and overall disease-free survival rates of 83% and 81%, as opposed to 66% and 58% for patients with Hb levels <12 g/dl (p=0.04 and p=0.02). The 5-year pelvic disease-free survival rate for stage II disease was 89% compared with 45% for stage III (p=0.006).

Conclusion. A mid-treatment Hb level of ≥12 g/dl was associated with significantly improved control of pelvic disease and improved 5-year pelvic disease-free and overall survival. Disease stage was an independent prognostic factor.

A fall in haemoglobin (Hb) level is common in patients with cancer and can be a direct effect of the disease as well as result from cancer-related therapy. The bone marrow is extremely radiosensitive, to the extent that some injury is produced by any radiation dose.[1] The radiation dose, treatment volumes and radiation dose rate all affect the acute response of the bone marrow to therapy. When small fields comprising 10 - 15% of the marrow are irradiated, the unexposed bone marrow responds by increasing its population of progenitor cells to meet the demands for haematopoiesis.[2,3] A high proportion of cancer patients undergoing radiotherapy are anaemic before or during treatment.[4] By decreasing the oxygen-carrying capacity of the blood, anaemia may result in tumour hypoxia and have a negative influence on the outcome of radiotherapy for various malignancies, as well as on quality of life.[5,6] A Hb level of 12 - 14 g/dl has been suggested as optimal for adequate oxygenation status of the tumour.[2]

The aim of this study was to determine the effect of Hb level at the start of treatment and mid-treatment on the response to treatment, local control, and pelvic disease-free and overall disease-free survival. The magnitude of the fall in the Hb level during treatment was also studied.

Material and methods

Seventy-two patients with carcinoma of the cervix accepted for radiation therapy in the Division of Radiation Oncology at Johannesburg Hospital between January and December 2002 were entered into this prospective study. The patients gave informed consent for participation in the study. Hb levels were measured immediately before the start of radiation therapy and in the middle of treatment, using a Hemocue photometer and microcuvettes provided by Schering Plough for the study. Forty-three patients (60%) had stage II disease and remaining 29 (40%) stage III disease. The patients received planned radiation therapy with external beam to the pelvis and intracavitary brachytherapy using an HDR selectron system. The patient and treatment characteristics are set out in Tables I and II.

Concomitant chemotherapy together with radiation was prescribed for 45 patients (62%). Cisplatin 30 - 35 mg/m^2 as an intravenous injection was prescribed weekly as a radiosensitiser along with radiation. The patients received a mean of 2 cycles (range 1 - 5 cycles) of chemotherapy along with radiation. Eighteen patients (40%) received 3 or more chemotherapy cycles. A fall in white cell count was the main reason for patients not receiving weekly chemotherapy as planned after the first cycle. Twenty-seven patients did not receive concurrent chemotherapy with radiation, for the following reasons: (*i*) hypo-fractionated treatment protocol of 4 Gy twice weekly (11 patients); (*ii*) HIV positivity (7 patients); (*iii*) low creatinine clearance (5 patients); (*iv*) low white cell count (2 patients); and (*v*) age (78 and 86 years, 2 patients).

Eight patients did not receive brachytherapy (3 did not receive the last fraction of external beam radiation, 3 had poor responses to external beam radiation, 1 was given an external boost due to advanced disease, and 1 died after external beam radiation).

Table I. Patient characteristics

Total No.	72
Age group (median 50.5 years)	
<50.5	36
>50.5	36
Stage	
IIB	43
IIIB	29
HIV	
Positive	9
Negative	63

Table II. Treatment parameters

External beam radiation dose (24.7 - 56.4 Gy, median 45.6 Gy)	
≤45.6Gy	57
>45.6 Gy	15
Dose/fraction (1.9 - 4 Gy/fraction, median 1.9 Gy)	
≤1.9 Gy/fraction	58
>1.9 Gy/fraction	14
Field size (238 - 408 cm^2, median 304 cm^2)	
≤304 cm^2	34
>304 cm^2	38
Brachytherapy dose (0 - 25 Gy, median 24.5 Gy)	
Nil	8
21 Gy	19
25 Gy	45
Concomitant chemotherapy	
Given	45
Not given	27

Statistical analysis

The mean mid-treatment Hb level was compared with the pre-treatment level using the paired-sample *t*-test. Fisher's exact test was used to compare the number of patients who had a drop in Hb levels according to various treatment parameters. The response to treatment and local control were compared between patients with an Hb level <12 g/dl and those with a level ≥12 g/dl using the chi-square test. Disease-free survival was calculated from the first day of treatment to failure either locally or at a distant site. Survival was analysed using the Kaplan-Meier method and prognostic variables were compared using the log rank test.

Results

The mean Hb level before radiation treatment was 12.8 g/dl (range 8.9 - 16.1 g/dl) and the mid-treatment level was 12.1 g/dl (9.7 - 16 g/dl). This fall in Hb level was statistically significant according to the paired-sample *t*-test ($p<0.0001$). The Hb level had fallen by mid-treatment in 78% of patients. The drop in Hb level was not affected by total dose of radiation, dose per fraction, treatment volume of external beam radiation, or chemotherapy versus no chemotherapy.

Patients were grouped into those with Hb levels <12 g/dl and ≥12 g/dl at the start of treatment for data analysis. There were no other significant differences between the two groups, as can be seen from Table III.

Response assessment

The response to radiation therapy was assessed clinically at completion of treatment and at follow-up after 2 months and by a Pap smear at 6 months. Responses were graded as complete (65 patients, 90%), partial (3 patients, 4%) or poor (3 patients, 4%). One patient (1%) had progressive disease. Patients who received chemotherapy had a significantly better response than those who did not ($p=0.04$). No significant correlation was demonstrated between response to treatment and pre-treatment or mid-treatment Hb level (<12 g/dl or ≥12 g/dl) ($p=0.5$). There was no significant correlation between stage of disease and response to treatment ($p=0.09$) (Table IV).

Treatment failures

Treatment failed in 13 patients. Nine patients had disease in the pelvis only, 3 had distant disease (1 each in liver, abdominal wall scar and supraclavicular node), and 1 had both local and distant disease (in the lung).

Of the 42 patients with mid-treatment Hb levels ≥12 g/dl 3 (7%) had pelvic failures, in comparison with 7 out of 30 patients (23%) with Hb levels <12 g/dl ($p=0.05$). The rate of overall treatment failure was also lower with mid-treatment Hb levels of ≥12 g/dl ($p=0.03$). However, the pre-treatment Hb level had no significant impact on treatment failure. Pelvic failures were noted in 7 of

Table III. Patient and treatment characteristics

		Hb <12 g/dl	Hb ≥12 g/dl	*p*-value
Age group (median 50.5 years)		11	25	0.29
≤ 50.5	36	8	28	
>50.5	36			
Stage				
IIB	43	3	40	0.28
IIIB	29	4	25	
External beam radiation dose (24.7 - 56.4 Gy, median 45.6 Gy)				
≤45.6 Gy	57	14	43	
>45.6 Gy	15	5	10	0.35
Dose/fraction (1.9 - 4 Gy/fraction, median 1.9 Gy)				
≤1.9Gy/fraction	58	15	43	0.53
>1.9 Gy/fraction	14	4	10	
Field size (238 - 408 cm^2, median 304 cm^2)				
≤304 cm^2	34	8	26	0.41
>304 cm^2	38	11	27	
Brachytherapy dose (0 - 25 Gy, median 24.5 Gy)				
Nil	8	2	6	0.27
21 Gy	19	2	17	
25 Gy	45	3	42	
Concomitant chemotherapy				
Given	45	4	41	0.52
Not given	27	3	24	

Table IV. Response according to parameters

	Complete	Partial	Poor	Progressive	*p*-value
Pretreatment Hb					
<12 g/dl	6	0	1	0	0.5
≥12 g/dl	59	3	2	1	
Mid-treatment Hb					
<12 g/dl	26	1	2	1	0.5
≥12 g/dl	39	2	1	0	
Stage of disease					
IIB	41	1	0	1	0.09
IIIB	24	2	3	0	
Chemotherapy					
Given	44	1	0	0	0.03
Not given	21	2	3	1	

29 (24%) patients with stage III disease and 3 of 43 (7%) with stage II disease (p=0.04).

Pelvic disease-free survival

The 5-year pelvic disease-free survival rate for the group as a whole was 76%. The disease-free survival for patients with a mid-treatment Hb level ≥12 g/dl was 83.5% compared with 66% for those with a level <12 g/dl (p=0.04) (Fig. 1). The 5-year pelvic disease-free survival rate was 84% for the 45 patients who received chemotherapy and 49% for the 27 patients who did not (p=0.07) (Fig. 2), and it was 89% for stage II disease and 45% for stage III disease (p=0.006) (Fig. 3).

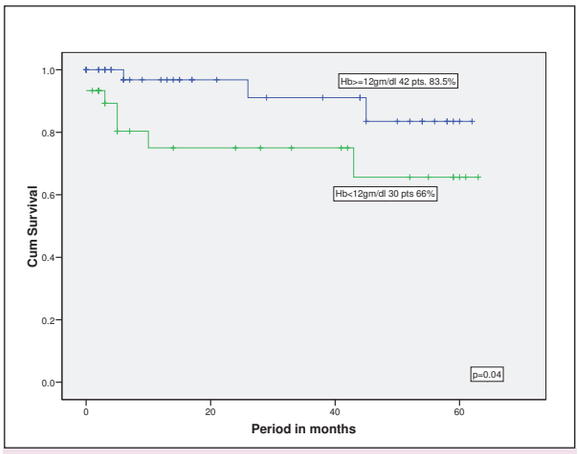

Fig. 1. Pelvic disease-free srvival versus mid-treatment haemoglobin in patients with carcinoma of the cervix.

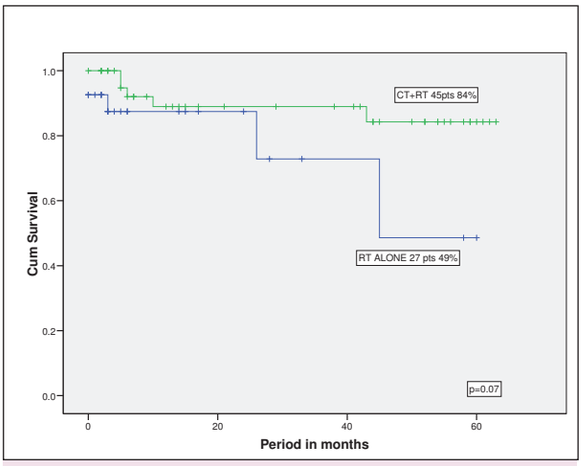

Fig. 2. Pelvic disease-free survival versus concomitant chemotherapy and radiotherapy in patients with carcinoma of the cervix.

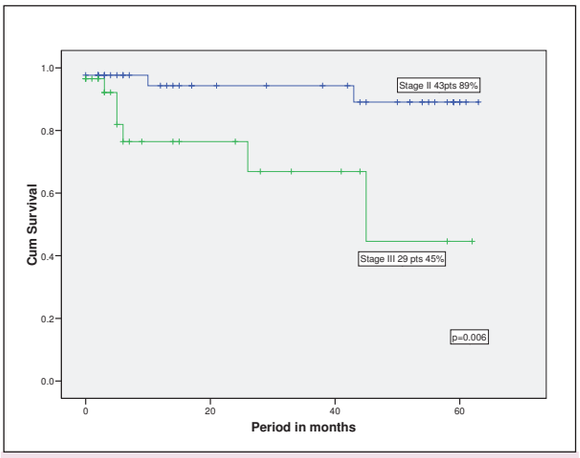

Fig. 3. Pelvic disease-free survival versus stage in patients with carcinoma of the cervix.

Overall disease-free survival

Four patients developed metastatic disease (1 each in supraclavicular node, liver, lung and abdominal wall scar). The 5-year overall disease-free survival rate for the group as a whole was 72%.

Patients who received chemotherapy had a 79% 5-year overall disease-free survival rate, as opposed to 46% for patients who did not receive chemotherapy (p=0.08). The mid-treatment Hb level appeared to affect overall disease-free survival in a similar way to pelvic disease-free survival, with rates of 81% for the group with Hb levels ≥12 g/dl and 58% for those with Hb levels <12 g/dl (p=0.02).

The 5-year overall disease-free survival rates for stage II and stage III disease were 89% and 37% respectively (p=0.00).

Discussion

Radiation therapy for cancer involves the exposure of a significant volume of bone marrow to high-energy photons. The ability of the patient to tolerate therapy is determined by haematological factors which reflect the potential of stem cells in the marrow to repair the damage as well as to repopulate the marrow component.[2,3] Approximately 50% of cancer patients undergoing radiation therapy are anaemic before or during treatment. By decreasing the oxygen-carrying capacity of the blood, anaemia may result in tumour hypoxia and have a negative influence on the outcome of radiotherapy for various malignances, even for small tumours not normally assumed to be hypoxic. Anaemia also has a negative effect on quality of life of cancer patients as evidenced by increased fatigue.[4]

Oxygenation status is affected by Hb level. Hypoxia and anaemia make solid tumours resistant to sparsely ionising radiation and chemotherapy.[5] Blomher *et al*.[6] suggested that anaemia may be a significant independent prognostic factor for treatment response and survival in cancer patients treated with chemotherapy or radiotherapy. The optimal pre-treatment Hb with regard to tumour oxygenation status is between 12 and 14 g/dl.[2] The mean pretreatment Hb of 12.8 g/dl in this study did not affect response to treatment or survival. Grogan *et al*.[7] studied the impact of anaemia and blood transfusions on 605 patients with carcinoma of the cervix treated with radiation therapy. The 5-year survival rate was 74% for patients who maintained an average Hb level of >12 g/dl as opposed to 52% for <12 g/dl and 45% for <11 g/dl (p=0.001). The authors also reported a significant reduction in both pelvic and distant recurrence (p<0.001 and p<0.006, respectively). Obermair *et al*.[8] reported progression-free survival rates for 60 patients with stage II to IV cervical cancer treated with chemo-radiation. The 5-year progression-free survival rate was 48% in patients with a Hb level >12 g/dl during treatment and 39% for those with an Hb level <12 g/dl (p<0.0002). They did not find the pretreatment Hb level to be a significant prognostic factor. In our series, the overall disease-free survival rate was 79% for patients who received chemo-radiation in comparison with 46% for those who received only radiation therapy (p=0.08). Of

the 27 patients who did not receive chemotherapy, 11 received a twice-weekly palliative treatment regimen, 7 were HIV positive, 5 had low creatinine clearances, 2 had low white cell counts and 2 were excluded because of age. These factors probably contributed to the poorer outcome.

Thomas[9] reported significantly lower rates of overall relapse, local recurrence and distant metastases in patients with an average mid-treatment Hb level ≥12 g/dl – they had a 5-year pelvic disease-free survival rate of 83% as opposed to 66% for patients with levels <12 g/dl (p=0.04), and a 5-year overall disease-free survival rate of 81% as opposed to 58% (p=0.02).

We assessed the response to radiation therapy clinically at completion of treatment and at follow-up after 2 months and with a Pap smear at 6 months. Responses were graded as complete (65 patients, 90%), partial (3 patients, 4%) or poor (3 patients, 4%). One patient had progressive disease. Patients who received chemotherapy had a significantly better response than those who did not (p=0.04).

Kapp *et al*.[10] reported improved control of pelvic disease (p=0.02) and a trend towards increased disease-specific survival (p=0.06) for patients whose Hb level increased after red blood cell transfusion. The rate of local control was 93% for patients with a mid-treatment Hb level ≥12 g/dl as opposed to 67% for those with a level <12 g/dl (p=0.05) in the present series.

Choi *et al*.[11] suggested in a study of 85 patients with carcinoma of the cervix that maintaining the Hb level above 10 g/dl during treatment was associated with better survival (p=0.005), especially in patients with lymph node involvement.

In our study the mean Hb level was significantly lower at the middle of treatment than before treatment. This fall was not significantly affected by total dose of radiation, dose per fraction, treatment volume of external beam radiation and chemotherapy versus no chemotherapy. Harrison *et al*.[12] reported a significant fall in Hb levels in patients undergoing radiation therapy for prostate, cervix and colorectal cancers, and Kenneth *et al*.[13] reported that stage of disease was associated with a fall in Hb levels during radiation for prostate cancers. In contrast, stage of disease was not found to affect the fall in Hb levels in the present series. Dalton *et al*.[14] reported that nearly two-thirds of patients receiving chemotherapy for various malignancies become anaemic during treatment. In the present series, chemotherapy did not have a significant impact on Hb levels.

Conclusions

This study showed that patients with mid-treatment Hb levels ≥12 g/dl had better local control as well as pelvic and overall disease-free survival than those with lower Hb levels. Our results are in concordance with the available literature. It is recommended that the mid-treatment Hb level should be measured in all patients receiving radiation therapy for carcinoma of the cervix. Blood transfusions are recommended if the level is <12 g/dl. Chemo-radiation resulted in a significantly higher disease-free survival rate. Stage of the disease was an independent prognostic parameter.

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