

The severity and optimal management of iron deficiency and anaemia before radiation for cervical cancer at the University of Pretoria Academic Hospitals

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Background: In patients with locally advanced cervical cancer who receive radiotherapy, outcomes correlate significantly with haemoglobin level before and during therapy. These patients often have severe anaemia and require repeated transfusions to achieve and maintain optimal haemoglobin levels.

Methods: Women with anaemia and cervical cancer needing primary radiation treatment were randomised to two groups: the study group received limited transfusion with intravenous and oral iron therapy; the control group received transfusion and oral iron. Haemoglobin (Hb) levels, transfusion and markers of iron status were recorded initially and during follow up.

Results: Forty-three participants were randomised; data for 39 were available for analysis: 19 received limited transfusion with parenteral and then oral iron (Fe group); 20 had allogenic transfusion and oral iron (Tf group). Average Hb levels in the Fe group displayed a steady rise over a 12-week follow-up while levels in the Tf group declined at about 0.5 g/dl per week. At week 12 pre-treatment levels were again reached despite intermittent transfusions.

Conclusions: Anaemic patients with late-stage cervical cancer in this setting have severe iron deficiency that necessitates aggressive correction before radiation. While patients with severe or critical anaemia and those who require radiation without delay need immediate transfusion, sufficient iron is critical to help replenish stores and sustain Hb levels. Patients with longer waiting times before radiation or less severe anaemia should have parenteral iron supplementation at the time of diagnosis and transfusion can be delayed until the time of radiation treatment.

Keywords: anaemia, cervical cancer, iron deficiency, iron status, radiation treatment

Background

Cervical cancer is the most common gynaecological malignancy in South African women between 15 and 44 years of age and almost 7 750 women are diagnosed each year.¹ The majority of patients present with locally advanced disease, which complicates treatment decisions and leads to a poor prognosis. While surgery is usually performed on patients with early-stage disease, locally advanced disease requires radiation with/without concurrent chemotherapy.

Anaemia is described as a reduction in red cell mass below the requirement to deliver the oxygen demand of the tissues. Haemoglobin (Hb) concentrate is used as marker and the World Health Organization (WHO) defines anaemia in women as an Hb < 12 g/dl.² Pre-treatment anaemia in cancer patients is common and treatment with surgery, chemo- and radiotherapy further impacts negatively. The mechanisms for anaemia in cancer patients are complex and include blood loss, haemolysis, myelosuppression, impaired red blood cell production and changes in iron metabolism.^{3,4} In South African patients with cervical cancer, important causes of anaemia before treatment probably include iron deficiency due to tumour bleeding, poor nutrition, renal impairment and HIV-related anaemia.

In cervical cancer patients who receive radiotherapy, outcomes correlate significantly with haemoglobin level before and during therapy. Low haemoglobin levels predict poorer disease control and survival^{5,6} and haemoglobin levels above 12 g/dl are crucial for good treatment response.⁷ Survival is improved when anaemia is corrected by transfusion and is then similar to patients who do not need transfusion to maintain normal haemoglobin.⁷ In our unit, cervical cancer patients therefore often receive

repeated transfusions to maintain normal haemoglobin levels and we have previously demonstrated that significant amounts of blood are utilised by these patients at a high cost.⁸ We do not, however, know the nature and severity of anaemia or the effectiveness of treatment, and limited information is available concerning alternative treatment options.

Pre-radiation management options for anaemia include limiting the blood loss, oral or parenteral haematinics, erythropoietin, transfusion and a combination of these strategies. Classical studies describing the effect of anaemia on radiation outcomes were mostly conducted in high-resource countries, presumably with short waiting times before treatment. Most of these understandably describe transfusion as the only treatment option as it immediately elevates haemoglobin and possibly tumour oxygenation, which is known to improve radiation response.⁷ In a more recent review only transfusion, erythropoietin and oral iron are discussed.⁹ Doubts about the safety of erythropoietin for patients with active neoplasms and high treatment costs, however, preclude its routine use in our setting.^{9,10}

No published guidelines for parenteral iron as treatment for anaemia could be found and the effectiveness was untested. Shortly after conceptualising this study, a research report described parenteral iron in a low dosage of 200 mg iron sucrose as effective to prevent anaemia in cervical cancer patients.¹¹

We hypothesised that anaemic cervical cancer patients in the developing world have severe iron deficiency and that parenteral iron is a suitable treatment option to correct anaemia before the onset of radiation therapy. This study first aimed to determine

the severity and nature of anaemia and iron deficiency among cervical cancer patients presenting with a haemoglobin level below 12 g/dl. In addition, two approaches to achieve and maintain optimal haemoglobin levels were studied and compared regarding effectiveness and safety. *P*-values of less than 0.05 were considered statistically significant. The study group received limited transfusion plus parenteral iron which was the experimental treatment, while the control group received transfusion and oral iron which was the standard treatment at the time.

Materials and methods

Patients from both University of Pretoria Academic Hospitals were recruited via the gynaecologic oncology clinics to this prospective randomised trial. The study protocol was reviewed and approved by the Research Ethics Committee of the Faculty of Health Sciences, University of Pretoria (83/2006).

Women with anaemia (laboratory haemoglobin value less than 12 g/dl) and cervical cancer needing primary radiation treatment (International Federation of Gynecology and Obstetrics (FIGO) stage IIB to IVB) were eligible to partake in the study. Women older than 70 years, those who did not or could not provide informed consent and those who were haemodynamically unstable or severely symptomatic were excluded from the study.

After recruitment according to the inclusion and exclusion criteria, information was provided and consent for study participation was sought. Patients were initially evaluated, local disease extent more than stage IB was confirmed by clinical examination and participants were randomised to one of the arms by means of sealed envelopes with instructions for treatment. All patients were then admitted to the gynaecology ward where the necessary special clinical and trial investigations (chest X-ray, kidney, liver and pelvic ultrasound, haematology and biochemical tests) were completed and they received further treatment. Data were collected on age, FIGO stage, initial iron, transferrin and transferrin saturation levels as well as pre-treatment haemoglobin level. All anaemia treatment complications were recorded.

The study group first received packed allogenic red cell transfusion (if needed) to increase the haemoglobin to 6 g/dl and then received intravenous iron sucrose therapy (Group A: Fe group). Total iron replacement dosage was calculated using the standard Ganzoni formula with target haemoglobin level of 13 g/dl and iron store needs of 500 mg.¹² Most patients received 1 g iron as this was our upper limit due to budget constraints. The latter also limited the number of patients recruited to this pilot study. The total iron dosage was given intravenously over two days according to our nephrology unit protocol because many of these patients have impaired renal function and prior to the study this was the only service unit with access to intravenous iron sucrose. Applying this protocol each 200 mg iron ampoule was diluted in 200 ml 0.9% m/v sterile sodium chloride (NaCl) solution and slowly infused over at least one hour.

Women in the control group received only allogenic blood transfusion to a corrected haemoglobin of at least 12 g/dl (Group B: Tf group). Transfusion needs were calculated as approximately two units of packed cells for every 2 g/dl that the haemoglobin had to be raised. All patients in both groups received standard oral iron supplementation upon discharge (ferrous fumarate 400 mg and folic acid 200 µg per day).

The waiting time before radiation could be started was about six weeks at the time of the study. Before the onset of radiation and two-weekly during treatment it was standard therapy to test haemoglobin and transfuse anaemic patients again to a haemoglobin level of at least 12 g/dl. Follow up of participants were planned for 3, 6 and 12 weeks after initial anaemia treatment irrespective of the initiation date of radiation. Haemoglobin levels were again recorded at these visits and data were collected on the need for further transfusion and the number of units transfused.

Results

Forty-three patients were recruited to the study, four were excluded from further analysis: two had incomplete data, one had an anaphylactic reaction to packed red cells and another patient died shortly after admission due to very advanced disease and kidney failure. Thirty-nine participants remained, of whom 19 received limited transfusion followed by parenteral and then oral iron (Group A: Fe group) and 20 had allogenic transfusion and oral iron (Group B: Tf group).

The median age of the participating women was 49 years (mean age 49.3 years) and FIGO staging of the participants ranged from IIB to IVB as per inclusion criteria with by far the largest group in stage IIIB. Both characteristics are typical of the distribution seen in the developing world and were similar for the two groups (Table 1).

Average pre-treatment serum iron levels were very low and more than 90% of all participants had severely decreased levels (< 7 mmol/l). Transferrin levels were mostly within the normal range, while transferrin saturation levels mimicked the iron levels. All participants were anaemic as per inclusion criteria and 29 women were severely anaemic with Hb < 10 g/dl. All differences in serum iron, transferrin, transferrin saturation and haemoglobin levels between the two groups were statistically non-significant ($p > 0.05$) (Table 2).

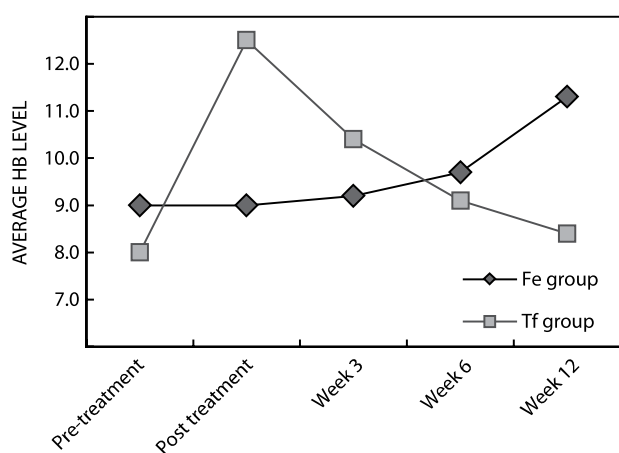
Low mean values of corpuscular volume as well as corpuscular haemoglobin were identified in all patients, which is indicative of microcytic, hypochromic anaemia and supports the diagnosis of iron-deficiency anaemia. On average patients in the Tf group received a further 3.4 units of packed red cells and the Fe group 2.9 units (range 2–4 units in both groups) after the initial treatment. While no adverse events occurred in the iron group, one patient in the transfusion group showed an anaphylactic reaction to packed red cells and was excluded from further analysis (data not shown).

Table 1: Demographic characteristics of the two study groups

Factor	Group A: Fe group, n = 19	Group B: Tf group, n = 20	All participants, n = 39
Mean age: years (range)	50.7 (38–61)	48.0 (31–71)	49.3 (31–71)
FIGO staging: n (%)			
Stage IIB	2 (11)	3 (15)	5 (13)
Stage IIIA	1 (5)	1 (5)	2 (5)
Stage IIIB	11 (58)	10 (50)	21 (54)
Stage IV	1 (5)	2 (10)	3 (8)
Staging incomplete at study entry	4 (21)	4 (20)	8 (21)

Table 2: Pre-treatment iron studies and haemoglobin values

Factor	Laboratory normal range	Group A (Fe), n = 19		Group B (Tf), n = 20		p-value	All participants, n = 39	
		Average (range)	Below normal (%)	Average (range)	Below normal (%)		Average (range)	Below normal (%)
Serum iron (mmol/l)	10–30	5.2 (1.8–15.2)	17/18 (94)	3.3 (1.0–12.0)	16/17 (94)	0.07	4.3 (1.0–15.2)	33/35 (94)
Transferrin (g/l)	2.0–3.6	2.2 (1.3–4.8)	9/19 (47)	2.1 (1.0–3.3)	10/18 (56)	0.72	2.2 (1.0–4.8)	19/37 (51)
Transferrin saturation level (%)	20–50	9.9 (1.0–37)	16/17 (94)	6.6 (2.0–18)	17/17 (100)	0.17	8.3 (1.0–37)	33/34 (97)
Haemoglobin (g/dl)	12.0–16.3	9.0 (5.3–11.9)	19/19 (100)	8.0 (5.1–11.4)	20/20 (100)	0.10	8.5 (5.1–11.9)	39/39 (100)

**Figure 1:** Average haemoglobin levels after limited transfusion with intravenous iron therapy (Fe group) or transfusion only (Tf group) over the study period.

Analysis of average haemoglobin levels before and after treatment and at weeks 3, 6 and 12 weeks of follow-up indicated a steady rise of haemoglobin in the Fe group. After immediate transfusion to at least 12 g/dl, levels in the Tf group showed a steady decline of about 0.5 g/dl per week; pre-treatment levels were again reached at 12 weeks despite intermittent transfusions in this group (Figure 1). At week 6, when radiation was usually started, an average 3 g/dl of haemoglobin had already been lost per patient.

Discussion

The vast majority of patients with inoperable cervical cancer presented with very advanced disease (FIGO stage IIIB or more), which is in accordance with similar findings in developing countries.^{13–15} The study recruited 43 consecutive locally advanced cervical cancer patients with haemoglobin levels below 12 g/dl and we found severe anaemia in most women, mostly microcytic.

In this study population, women had severely depleted iron stores. Serum iron levels and transferrin saturation, indicators for total and biologically available iron, were both markedly reduced in almost all patients making fast replenishment with oral iron supplements unlikely.^{16,17} Good average transferrin levels and normal transferrin levels in about half of all participants suggest that our patients had a reasonable nutritional status¹⁸ and the finding does not support the assumption that poor nutrition contributes in a major way to anaemia. Only one patient had normal transferrin saturation, underlining the severity of the iron deficiency.

Comparing the effect of the two treatment strategies, aggressive transfusion had an immediate but short-lived effect that was worse than the expected average lifespan of about 50–60 days for transfused red cells.¹⁹ It is known that this lifespan is adversely affected by several factors including longer storage time, and that about 20–25% red cells is lost in the first 24 hours. Limited transfusion (Hb ~ 6 g/dl) combined with parenteral iron treatment led to a slow but steady increase in haemoglobin level, sustained over the study period. Both strategies were relatively unsuccessful in correcting anaemia by the time of the radiotherapy appointment (six weeks) in that both groups had increased their average haemoglobin level by only about 1 g/dl. At 12 weeks the blood transfusion group had lost almost all the effects of the transfused blood and were back at pre-treatment values, but the parenteral iron group had a clear advantage and a very significant improvement of haemoglobin.

These findings demonstrate that high-dosage parenteral iron replacement therapy is much more successful in correcting severe anaemia in cervical cancer patients and that bioavailability of iron from transfused blood is probably limited.²⁰ If radiation treatment starts later than three weeks after transfusion, most of the effect is lost and blood transfusions need to be repeated.

In the current study, in the transfusion arm, oral iron supplementation was not effective, probably because larger dosages are required, intestinal absorption and compliance is usually poor and too much time is needed to correct the anaemia with this approach.²¹ Parenteral iron, on the other hand, was much more effective, improved haemoglobin levels steadily and corrected anaemia at 12 weeks from treatment.

In addition to the known drawbacks of blood products like high price, safety concerns and negative effects on immunity,^{22,23} our data show that the correction of haemoglobin levels by red cell transfusion is very short-lived in late stage cervical cancer patients. We also demonstrate that parenteral iron was more effective than blood transfusion but relatively slow to correct anaemia.

Based on these results and existing literature, it is clear that anaemia among cervical cancer patients in developing countries requires more aggressive management. We suggest the following management protocol until further results become available to improve the calculation of iron needs.

- Evaluate and manage:
 - kidney function and potassium levels;
 - haemoglobin and platelets;
 - hydration and haemodynamics;
 - tumour size, stage and active bleeding.

- Transfuse red blood concentrate:
 - if clinically needed.
 - Transfusion targets/triggers:
 - Healthy and young: Hb 8 g/dl;
 - Frail or older: Hb 10 g/dl;
 - Before radiation: Hb 12 g/dl;
 - Limit transfusion to two units per day.
- Infuse parenteral iron:
 - calculate need using Ganzoni formula;
 - alternatively infuse 1 000 mg elemental iron per patient.
- Prescribe extra haematinics:
 - intramuscular injection of vitamin B12 or orally daily (0.4 mg per day);
 - oral folic acid (at least 0.4 mg per day);
 - oral elemental iron 120 mg per day with vitamin C tablets.
- Check haemoglobin before radiation:
 - correct by transfusion;
 - Hb target 12 g/dl.
- Minimum two-weekly Hb check and optimise to > 11 g/dl.

The study had some weaknesses. Many patients did not have data at all the follow-up points for reasons that included travel distances and cost, and a shortage of hospital beds for non-critical patients. Data on ferritin levels were unfortunately too incomplete to allow incorporation into analysis, although this marker of iron stores may be influenced by an acute-phase reaction. We did not investigate the contribution of renal impairment to anaemia or iron and folic acid levels after treatment, thus cannot comment on optimal dosage of haematinics. The study did not aim to investigate treatment outcomes.

Conclusion

This study demonstrates that anaemic patients with late-stage cervical cancer have severe iron deficiency that necessitates aggressive correction before radiation treatment starts. Oral iron supplementation is probably insufficient for most patients, while parenteral iron corrects iron-deficiency anaemia before or by 12 weeks.

Patients with severe or critical anaemia and those who will start radiation soon should have immediate transfusion in combination with parenteral iron to help correct and then sustain haemoglobin at required levels. We suggest that units with longer than two-week waiting times for radiation appointments should use parenteral iron supplementation at the time of diagnosis and should then delay transfusion to the time of radiation appointment. The careful calculation of iron needs in these severely depleted patients requires more attention to improve response for both parenteral and oral iron treatment. Further investigation on the role of renal impairment, control of further blood loss and need for other haematinics in these patients is essential to improve our current treatment strategies.

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