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Effects of radiation and total androgen blockade on serum hemoglobin, testosterone, and erythropoietin in patients with localized prostate cancer

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ABSTRACT

Objective

The objective of the present study was to evaluate the incidence, time of onset, and extent of hemoglobin, testosterone, and erythropoietin changes in patients with localized prostate cancer receiving either radiation alone or radiation combined with total androgen blockade (TAB).

Methods

The study enrolled 35 patients (median age: 69 years) with clinically localized prostate cancer who received 3-dimensional conformal radiation with or without TAB. Patients were generally treated with radiation alone (group 1), radiation plus short-term (≤6 months) TAB (group 2), or radiation plus long-term (≥2 years) TAB (group 3). Serum hemoglobin, testosterone, and erythropoietin in these patients were prospectively evaluated.

Results

The mean baseline serum hemoglobin for group 1 (n = 20), group 2 (n = 6), and group 3 (n = 9) was 149 g/L, 153 g/L, and 143 g/L respectively. We observed no significant decline in serum hemoglobin, testosterone, or erythropoietin among patients treated with radiotherapy alone. A significant drop in serum testosterone was noted in the group 2 and 3 patients within 1 month ($p < 0.001$), reaching a plateau at approximately 6 months. That change was followed by a significant decline ($p < 0.001$) in serum hemoglobin at 3–6 months (137 g/L in group 2 and 129 g/L in group 3). We observed a small but statistically significant increase in serum erythropoietin ($p < 0.001$) of 8 U/L in group 2 and 4 U/L in group 3 after 6 months of TAB. No immediate recovery in serum hemoglobin, testosterone, or erythropoietin was observed upon completion of TAB.

Conclusions

Although conformal radiotherapy alone for localized prostate cancer had no effect on serum hemoglobin, testosterone, or erythropoietin, TAB led to a significant decline in testosterone, which was followed by decline in hemoglobin that was not a result of a deficiency of erythropoietin.

KEY WORDS

Prostate cancer, anemia, radiotherapy, total androgen blockade

1. INTRODUCTION

Prostate cancer is the most common malignancy among North American men, and radiation and total androgen blockade (TAB) are commonly used treatment options. In metastatic prostate cancer, TAB is considered first-line treatment; it is also used in the treatment of both locally advanced and recurrent prostate cancer[1,2]. Although not routinely recommended as first-line therapy for the management of early-stage prostate cancer, TAB is increasingly being used for clinically localized prostate cancer as well[3]. The benefit of TAB in addition to radiotherapy has been demonstrated in the treatment of high- and intermediate-risk localized prostate cancer[4,5], but its role in earlier-stage disease remains controversial and is an area of active clinical research.

Some well-known toxicities are associated with TAB. It has long been known that anemia can develop in patients undergoing orchiectomy, which was the first form of TAB, albeit surgical. Serum testosterone was found to decline significantly within 10 days of orchiectomy and that decline in testosterone was followed by a decline in serum hemoglobin (approximately 10 g/L within 40 days)[6]. Newer approaches to TAB have largely included the use of luteinizing hormone–releasing hormone (LHRH) agonists and antiandrogens that are thought to have similar

effects on serum testosterone and hemoglobin[1,7–10]. Recent studies have confirmed a decline in serum hemoglobin attributable to these newer approaches to TAB—and also a variety of other side effects, including metabolic disorders, cardiovascular disease, hot flashes, sexual dysfunction, depressed mood, muscle weakness, and osteoporosis[2,7,11–17].

Radiation therapy has also been associated with a decline in serum hemoglobin, although the degree of that decline for prostate cancer is uncertain, especially with respect to newer techniques, in which more localized volumes within the pelvis are treated[18]. It has generally been believed that a large volume of bone marrow needs to be treated with radiation before a significant effect on hemoglobin is noticed. It has therefore been assumed that, when patients with clinically localized prostate cancer are treated with a combination of restricted radiation and TAB, the development of anemia is related to hormonal effects rather than to radiation. The mechanism by which anemia occurs is uncertain[16], and the role of erythropoietin as the most potent hematopoietic factor remains ambiguous. In the few published studies, no dramatic effect on serum erythropoietin has been observed after completion of TAB, but so far, no study has evaluated variation in erythropoietin during TAB itself. In fact, it remains to be determined how erythropoietin reacts to low serum testosterone and hemoglobin during the first few months after the start of TAB[19]. We therefore decided to prospectively evaluate the influence of radiotherapy—either alone or in combination with TAB—on serum hemoglobin, testosterone, and erythropoietin in patients with clinically localized prostate cancer.

2. METHODS

Patients with clinically localized prostate cancer were entered into the study after Research Ethics Board approval. All had histologic confirmation of prostate cancer, clinically localized disease with no evidence of distant metastases, an Eastern Cooperative Oncology Group performance status of 0–2, and a normal complete blood count. Patients with pre-existing anemia or liver or kidney disease were excluded from the study. Based on the risk stratification described by D'Amico *et al.*[20], the patients were divided into 3 groups: low-risk (group 1: treated with radiation alone for 2 months), intermediate-risk [group 2: treated with radiation plus short-term TAB (6 months or less)], and high-risk [group 3: treated with radiation plus long-term TAB (2 years or more)].

Radiation treatment was 3-dimensional conformal radiotherapy limited to the region of the prostate gland with or without the seminal vesicles, using a 6-field isocentric technique and a median dose of 76 Gy in 38 fractions delivered over 7.5 weeks. The pelvic lymph nodes were not treated[21]. The TAB initiated for the intermediate- and high-risk patients consisted of a combination of an antiandrogen and a LHRH agonist, started before radiotherapy. Bicalutamide was the most commonly used antiandrogen, and it was usually given daily for up to 6 months. Goserelin was the most commonly used LHRH agonist, and it was initiated approximately 2–3 weeks after the start of the antiandrogen and usually administered every 3 months for a total of 6–36 months depending on the physician's treatment recommendations.

Baseline laboratory evaluations for all patients included complete blood count, serum erythropoietin and testosterone, liver function tests, blood urea nitrogen, creatinine, and prostate-specific antigen. While on treatment, all blood work, including serum hemoglobin, testosterone, and erythropoietin, was performed at regular intervals (baseline, month 1, end of radiation, and months 3, 6, 9, 12, 18, 24, 30, 36, 42, 48) determined by the length of treatment in each group of patients. Follow-up blood work continued for 1–2 years after completion of therapy in each group of patients. Serum erythropoietin was determined at a centralized reference laboratory.

2.1 Statistics

For the analysis, we used the general linear model with serum hemoglobin, testosterone, and erythropoietin as the dependent variables. Two class variables—test timing and patient identification—were used as explanatory variables in the model. The patient identification variable was treated as a random effect, so that the results of the model could be generalized to the population and not just to patients in the dataset.

Although we initially planned to recruit 20 patients in each treatment group, slow accrual meant that we could not achieve our goal. Therefore, further to a random effects model analysis as previously described, we also performed a nonparametric analysis (Wilcoxon signed-rank test) to address concerns related to the small sample size.

3. RESULTS

Table I shows patient and disease demographics for the 35 patients (median age: 73 years) enrolled in the study (group 1: $n = 20$; group 2: $n = 6$; group 3: $n = 9$). All patients completed therapy and showed no evidence of recurrence during the study period. Group 2 patients remained on a continuous course of TAB for 6 months; group 3 patients also received continuous TAB, with 2 patients receiving 24 months and 7 patients receiving 36 months of treatment as recommended by the treating physician. No patient stopped TAB early because of side effects.

As shown in Table II, no significant changes in serum hemoglobin, testosterone, and erythropoietin were observed during or after treatment in the group 1 patients. That group, treated with radiation

TABLE I Patient characteristics by treatment group

Characteristic	*Group*[a]		
	1	*2*	*3*
Patients (*n*)	20	6	9
Median age (years)	72.5	77.5	74
Initial stage	T1c–T2a	T1c–T2a	T1c–T4
Baseline serum markers			
Hemoglobin (g/L)	149	153	143
Testosterone (nmol/L)	11	11	11
Erythropoietin (U/L)	11	9	12

[a] Group 1: radiation only; group 2: radiation and short-term total androgen blockade (median duration: 6 months) radiation and long-term total androgen blockade (median duration: 36 months).

TABLE II Variations in serum hemoglobin, testosterone, and erythropoietin in patients treated with radiation therapy alone (group 1)

Time point	*Hemoglobin (g/L)*	*Testosterone (nmol/L)*	*Erythropoietin (U/L)*
Baseline	149	11	12
Month 1	149	12	14
End of radiation	143	11	15
Month 3	147	14	12
Month 6	148	12	12
Month 9	148	12	14
Month 12	145	11	14
Month 18	149	12	12

therapy alone, served as a "control" group whose results were compared with those of groups 2 and 3, whose members received TAB in addition to radiation.

Table III shows the changes noted in group 2 patients—most notably a significant drop in serum testosterone ($p < 0.01$) to 3 nmol/L from a baseline value of 12 nmol/L that could be detected after 1 month of TAB. In that group, serum testosterone reached a nadir (1 nmol/L) at approximately 3 months and stayed fairly low until 12 months (2 nmol/L). Serum testosterone started to gradually increase at more than 6 months after completion of TAB, but it did not return to baseline during 18 months after completion of TAB. We also observed a statistically significant decline ($p < 0.05$) in serum hemoglobin at approximately 3 months after initiation of TAB, to 137 g/L from a baseline value of 153 g/L. Serum hemoglobin remained low for the first year after completion of TAB. Serum erythropoietin increased modestly during the first 6 months of treatment, reaching a maximum (18 U/L from a baseline of 9 U/L) that was also found to be statistically significant ($p < 0.05$). During the rest of the study, we observed minor fluctuations in serum erythropoietin, but that marker remained well above baseline for the duration of the study.

As noted in Table IV, the group receiving radiation plus long-term TAB showed a decline in serum testosterone after 1 month of TAB, to 5 nmol/L from 12 nmol/L at baseline ($p < 0.01$). That decline continued during the first 6 months of treatment and then reached a plateau, after which some minor fluctuations occurred. Subsequent to the decline in serum testosterone, 6 months after TAB was initiated, serum hemoglobin declined to 129 g/L from a baseline of 143 g/L ($p < 0.05$). Up to 1 year after completion of TAB, serum hemoglobin fluctuated slightly, but it remained below baseline. In this group of patients, serum erythropoietin rose during the first 6 months of treatment (to 16 U/L from 13 U/L), but the change did not reach statistical significance ($p > 0.2$). Serum erythropoietin remained above baseline throughout treatment with TAB.

TABLE III Variations in serum hemoglobin, testosterone, and erythropoietin in patients treated with radiation plus short-term total androgen blockade (group 2)

Time point	*Hemoglobin (g/L)*	*Testosterone (nmol/L)*	*Erythropoietin (U/L)*
Baseline	153	12	9
Month 1	147	3	13
Month 3	137	1	16
Month 6	139	1	18
Month 9	135	1	17
Month 12	134	2	16
Month 18	135	7	15
Month 24	135	7	17

TABLE IV Variations in serum hemoglobin, testosterone, and erythropoietin in patients treated with radiation plus long-term total androgen blockade (group 3)

Time point	*Hemoglobin (g/L)*	*Testosterone (nmol/L)*	*Erythropoietin (U/L)*
Baseline	143	12	13
Month 1	143	5	10
Month 3	139	2	15
Month 6	129	1	16
Month 9	134	1	15
Month 12	131	2	13
Month 18	128	1	15
Month 24	129	2	19
Month 30	132	3	13
Month 36	130	2	16
Month 42	125	3	—[a]
Month 48	131	2	—[a]

[a] Insufficient data for analysis.

Figure 1 shows the mean serum hemoglobin for all 3 groups of patients, permitting a comparison between patients who received and did not receive TAB. Figures 2 and 3 show how serum testosterone, hemoglobin, and erythropoietin changed from baseline during and after treatment for patients in groups 2 and 3 respectively.

Despite the small sample size, the observed drop in serum hemoglobin was substantial enough that it achieved statistical significance. Our analysis used a random-effects model to simultaneously model all time points within each group. Although that approach had the advantage of accommodating missing values at some of the later time points and of looking at the time course for all time points in a single model, it is perhaps also less transparent than a simpler test might have been.

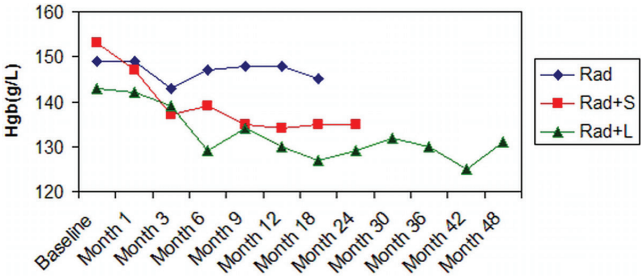

FIGURE 1 Variations in serum hemoglobin in 3 groups of patients: those receiving radiation alone [Rad (filled diamonds)]; radiation with short-term (S) total androgen blockade (filled squares); radiation with long-term (L) total androgen blockade (filled triangles).

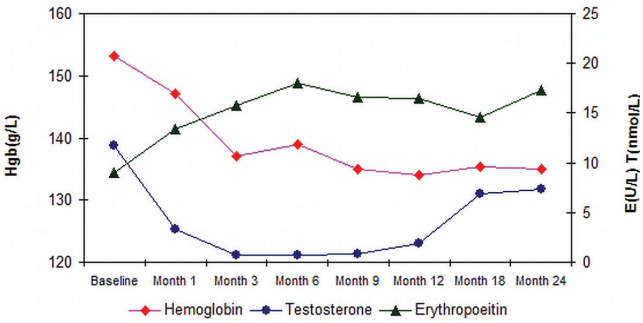

FIGURE 2 Variations in serum hemoglobin [Hgb (filled diamonds)], testosterone [T (filled circles)], and erythropoietin [E (filled triangles)] in patients treated with radiation plus short-term total androgen blockade.

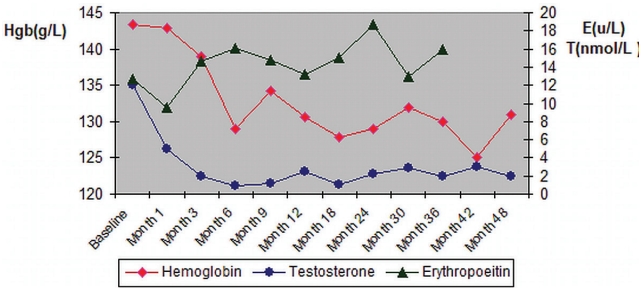

FIGURE 3 Variations in serum hemoglobin [Hgb (filled diamonds)], testosterone [T (filled circles)], and erythropoietin [E (filled triangles)] in patients treated with radiation plus long-term total androgen blockade.

The alternative analysis that follows may prove to be more convincing. In the radiation-only group, the observed change in serum hemoglobin from baseline to 6 months ranged from a drop of 13 g/L to an increase of 17 g/L. At that time point, 13 valid data points are available, and a Wilcoxon signed rank test and a *t*-test both failed to find a significant change. On the other hand, for the short-term TAB group, every single one of the 6 patients showed a drop in serum hemoglobin at 6 months. Those drops ranged from 6 g/L to 24 g/L. A Wilcoxon signed rank test found the change to be statistically significant at $p = 0.03$. Similarly, in the long-term treatment group, 7 valid measurements are available at 6 months, and all reflected a drop. Those drops ranged from 4 g/L to 34 g/L. A Wilcoxon signed rank test found the change to be statistically significant at $p = 0.02$.

Thus, although it might legitimately appear that our small sample size lacked the power to demonstrate a difference, the actual difference is so marked that we did indeed find it to be statistically significant.

4. DISCUSSION

Radiation and TAB are important components of treatment in the management of prostate cancer, and anemia is not usually prevalent at initial diagnosis. The development of anemia in these patients has therefore been a source of concern, although the exact causative factors remain to be determined. Anemia can influence the patient's quality of life, and it may even impair local control of prostate cancer treated by radiotherapy. Our study demonstrates the association between serum testosterone, hemoglobin, and erythropoietin in patients with localized prostate cancer who received radiation with or without TAB. We observed a significant difference in serum testosterone, hemoglobin, and erythropoietin, during and after treatment, between the 20 patients who received radiotherapy alone and the 15 patients who received a combination of radiation and TAB.

In group 1, patients showed no significant decline in serum testosterone, hemoglobin, and erythropoietin. That finding confirms the hypothesis that limited-field radiotherapy restricted to small volumes within the pelvis (specifically to the region of the prostate with or without the seminal vesicles) does not affect serum hemoglobin or testosterone[4]. A previous study[18] predicted that modern radiotherapy limited to the prostate should not result in significant hematologic toxicity, and our results are certainly in keeping with that theory. Also, as expected, we

observed no decline in serum erythropoietin in that group of patients.

In groups 2 and 3, who received radiation plus TAB, we observed a considerable decline in serum testosterone that became obvious at 1 month after the start of TAB. That decline seemed to plateau within 3–6 months after the start of TAB. Interestingly, serum testosterone remained low even 12 months after completion of TAB, suggesting a slow recovery even after just 6 months of that therapy. Subsequent to the testosterone decline in groups 2 and 3, serum hemoglobin dropped. That decline in serum hemoglobin became noticeable within the first 3–6 months after initiation of TAB, which accords with the results of earlier studies, in which declines in serum testosterone and hemoglobin were reported as a result of orchiectomy, LHRH monotherapy, and combined hormonal blockade. The degree of reduction in serum hemoglobin that we observed is similar to those reported in other studies and often did not result in clinically significant or laboratory-defined anemia even though serum testosterone was usually at castrate levels. Overall, there seemed to be a mean decline of 14 g/L (median: 14.5 g/L; standard deviation: 9 g/L; range: 2–34 g/L) in serum hemoglobin after 3–6 months of TAB, which is in keeping with the results of previous studies[22]. We also observed a modest increase in serum erythropoietin in patients treated with TAB (both short-term and long-term) occurring after the decline in serum hemoglobin and despite low serum testosterone. The increase in serum erythropoietin became statistically significant in group 2 (radiation with short-term TAB). Increased serum erythropoietin during the first 6 months after the initiation of TAB seems to be a response to the decline in serum hemoglobin rather than a cause for it. The results of present study therefore militate against previous assumptions that the drop in serum hemoglobin caused by TAB might be mediated by a decline in serum erythropoietin. The results of the present study are also consistent with those in older studies showing that even short-term TAB can lead to a significant decline in serum testosterone and hemoglobin, and that those markers can take from months to years after completion of therapy to fully recover[17]. Within patients in groups 2 and 3, serum testosterone and hemoglobin remained below baseline even up to 12 and 18 months after completion of TAB.

From the observed results, it can be postulated that TAB results in a fairly rapid drop in serum testosterone that is followed by a decline in serum hemoglobin, suggesting that the decline in testosterone is responsible for the reduction in hemoglobin. We originally hypothesized that the decline in testosterone might lower serum erythropoietin, which consequently could lower serum hemoglobin. However, our results indicate that a mechanism of that kind is not operating. In fact, serum erythropoietin increased, but still did not stop the decline in serum hemoglobin. Mechanisms independent of the erythropoietin system must therefore be operating for the decline in serum testosterone to be leading to lower serum hemoglobin.

Although some patients become clinically anemic after TAB, the drop in serum hemoglobin that we observed can lead to a wide range of effects. Still, most patients are still able to maintain a serum hemoglobin within the lower limits of normal identified in laboratories. Given that every study patient had clinically localized disease, a performance status of 0–2, and a normal complete blood count, and also given that patients with pre-existing anemia or liver or kidney disease were excluded from the study, the risk level of the patients did not seem to have an influence on the laboratory results.

Our study has some limitations, the most obvious being the relatively small sample size, especially for groups 2 and 3. We also could not control for other factors that might potentially be affecting serum hemoglobin, because the study was not randomized. Finally, because of protocol limitations, we could not evaluate whether lower serum hemoglobin in the patients affected qualify of life.

5. CONCLUSIONS

Our results indicate that localized radiotherapy on its own does not affect serum hemoglobin, testosterone, or erythropoietin. On the other hand, TAB has a profound effect on serum testosterone even within 1 month, and decline in serum testosterone is followed by a subsequent decline in serum hemoglobin and a rise in serum erythropoietin. A deficiency in erythropoietin does not appear to be the mechanism by which the decline in serum hemoglobin occurs. A better understanding of how TAB causes serum hemoglobin to decline is needed so that the reductions seen with this treatment can be better appreciated and managed.

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7. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to disclose.

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