How are hemoglobin levels affected by androgen deprivation in non-metastatic prostate cancer patients?

Richard Choo, MD,[1,2] Sarat Chander, MBBS,[1,3] Cyril Danjoux, MD,[1] Gerard Morton, MD,[1] Andrew Pearce, MD,[1] Gerrit Deboer, PhD,[1] Ewa Szumacher, MD,[1] Andrew Loblaw, MD,[1] Patrick Cheung, MD,[1] Tony Woo, MBBS[1]

[1]Department of Radiation Oncology, Toronto Sunnybrook Regional Cancer Centre, University of Toronto, Toronto, Ontario, Canada
[2]Mayo Clinic, Rochester, Minnesota, USA
[3]Wellington Cancer Centre, Wellington Hospital, Wellington, New Zealand

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Purpose: *To examine the change of hemoglobin in relation to testosterone level in non-metastatic prostate cancer patients receiving 2-year androgen suppression.*
Methods and materials: *A cohort of 72 patients, as participants of a phase II study, were treated with adjuvant radiotherapy plus 2-year androgen suppression after surgery to reduce the risk of relapse. Patients had laboratory tests including hemoglobin (Hb) and testosterone, and a quality of life questionnaire at regular intervals during the androgen suppression and post-androgen suppression period. The pattern of the change in Hb was evaluated in relation to testosterone level. The clinical significance of Hb change was assessed with a correlation analysis between Hb and the three domains of the questionnaire (global health status, physical functioning, and fatigue).*
Results: *Median age was 64.2 years. Median follow-up was 37 months. Mean Hb at the baseline was 148.4 g/L. It declined slightly with radiotherapy by 2.2 g/L. Maximal Hb decline during androgen suppression was 10.5 g/L ($p<0.0001$), occurring at 24 months after the initiation of androgen suppression. In most patients, Hb decline was < 20 g/L. In the post-androgen suppression period, the recovery of Hb was slow and followed that of testosterone. The three quality of life domains did not show any significant correlation with the change in Hb.*
Conclusion: *The decline and recovery of Hb was closely related to that of testosterone. Two-year androgen suppression resulted in a statistically significant decline of Hb, which had, however, no clinically apparent adverse effect on the three quality of life domains.*

Key Words: prostate cancer, anemia, hemoglobin, androgen suppression

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Address correspondence to Dr. Richard Choo, Division of Radiation Oncology, Mayo Clinic, 200 First Street SW, Rochester, Minnesota 55905 USA

Introduction

Androgen deprivation is quite widely used for the treatment of prostate cancer. Since Huggins et al[1] demonstrated in 1941 that orchiectomy or estrogen administration resulted in tumor regression in metastatic prostate cancer, androgen deprivation has been the mainstay for the management of metastatic prostate cancer. In recent years, the role of androgen deprivation has been expanded to the neoadjuvant and/or adjuvant setting where androgen deprivation is applied for a limited period of time in conjunction

with definitive primary therapy such as radical prostatectomy or radiotherapy. Since these patients (unlike those with metastatic disease) are usually long-term survivors, it has been increasingly important to address potential long-term adverse effects of prolonged androgen deprivation. One such effect is a decline of hemoglobin (Hb) leading to anemia, as the erythropoietic effect of androgens is deprived. The object of this manuscript is to examine the pattern and extent of Hb change in relation to testosterone level in prostate cancer patients receiving post-operative adjuvant radiotherapy plus 2-year androgen suppression.

Materials and methods

This report is based on the cohort of prostate cancer patients in a phase II study, evaluating the efficacy of a combined approach of post-operative adjuvant radiotherapy plus 2-year androgen suppression for those with adverse pathological features (such as positive resection margins and/or extra-capsular extension) after radical prostatectomy. The study was approved by the local Research Ethics Committee, and open for accrual between 1998 and 2002.

All the patients were treated with post-operative radiotherapy to the prostate bed and androgen suppression for 2 years. Radiation doses and fractionation schedules were 6000-6600 cGy in 30-33 fractions over 6-6.5 weeks. The target volume of radiotherapy was small and limited to the prostate bed and periprostatic tissue. No attempt was made to treat regional pelvic lymph nodes. Androgen suppression started within 2 weeks after the completion of radiotherapy. It consisted of nilutamide 100 mg three times a day orally for only 4 weeks and busereline acetatate 6.3 mg depot subcutaneously every 2 months for 2 years. Nilutamide was given 1-2 weeks prior to the first injection of busereline acetate depot. Chronic administration of busereline acetate, a synthetic peptide analog of gonadotrophin releasing hormone (GnRH), ensures continuous suppression of testosterone secretion.

Baseline laboratory investigations prior to the therapeutic intervention included serum prostate specific antigen (PSA), complete blood count (CBC), and testosterone. These tests were repeated 2-4 weeks after the completion of radiotherapy (just prior to the initiation of busereline acetate), then every 4 months during the 2-year androgen suppression, and every 6 months thereafter. The parameters that we particularly analyzed for this report were serum Hb, hematocrit, mean corpuscular volume (MCV), platelet count, and testosterone. We carefully examined the patient records to determine if there were any co-morbidities or events that could influence the baseline or subsequent Hb levels. Pre-existing medical conditions, surgical interventions or post-treatment complications such as rectal and/or urethral bleeding were recorded, and their nature and severity were assessed. When a patient was judged to have any confounding factor affecting Hb level significantly over a long term, he was excluded from the analysis. However, when the effect was temporary and limited only to the laboratory results at the time of the event (e.g. knee surgery), only the affected readings were excluded from analysis. When patients received less than the prescribed course of 12 busereline acetate injections (10 patients), all the laboratory results up to the date of last injection were included.

Patients completed the EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer, Quality of Life questionnaire version 3.0) with the added prostate cancer specific module at each visit for the evaluation of the quality of life. In order to assess the potential impact of Hb change on the quality of life, we examined the changes in the scores of the three specific domains of the questionnaire in relation to Hb. These domains are Global Health Status, Physical Functioning (Functional Scales) and Fatigue (Symptom Scales). The details of the survival outcomes, quality of life evaluation, and other endpoints of the study are beyond the scope of this manuscript, and will be reported separately.

Statistical analysis

Mean Hb, MCV, hematocrit, platelet and testosterone values were calculated for each visit. The two-tailed t-test was used to test for significance of change of these laboratory parameters with radiotherapy and androgen suppression. The mean scores of the three quality of life domains were calculated at each visit, and then the changes of these mean scores from the baseline were computed for each domain. Potential impact of Hb change on the quality of life was assessed by Pearson's correlation coefficient between the scores of the three domains and Hb values at each visit and for each patient individually.

Results

The study was closed in April 2002 and accrued a total of 79 patients. All patients had the histologic diagnosis of adenocarcinoma of prostate, pathological T3 and/or positive resection margins, and no evidence of nodal or distant metastasis. Median interval

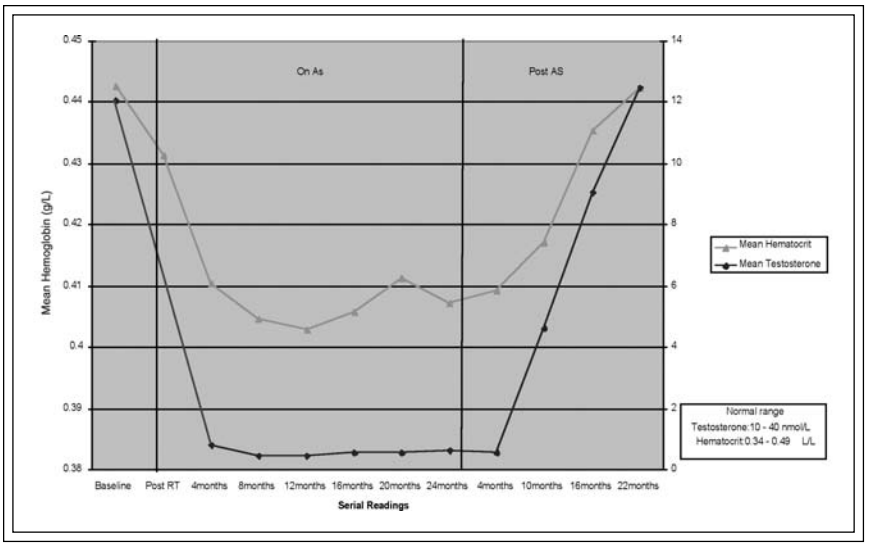

Figure 1. Mean hemoglobin (Hb) with standard error bars and mean testosterone at serial follow up visits. AS: androgen suppression, n: number of patients.

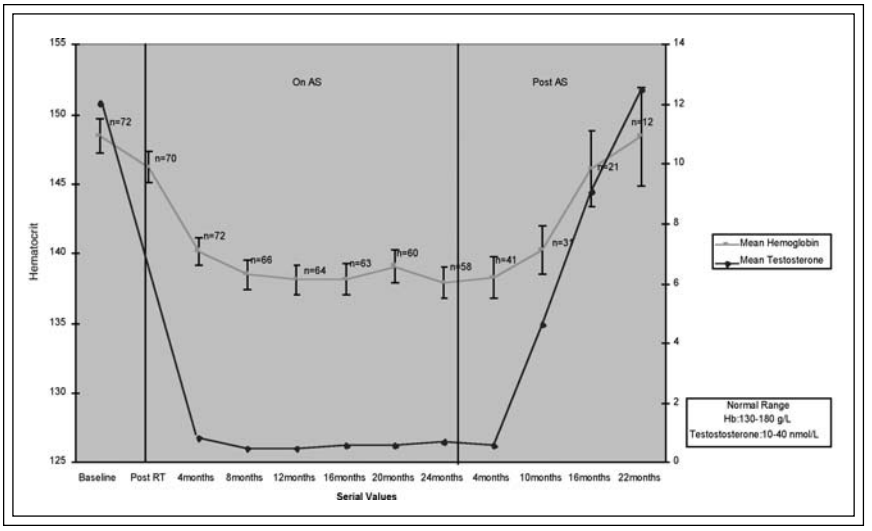

Figure 2. Variation of mean hematocrit and mean testosterone at serial follow-up visits. AS: androgen suppression.

between radical prostatectomy and post-operative radiotherapy was 4.23 months.

Seventy-two patients were identified as eligible for the analysis of the effect of 2-year adjuvant androgen suppression on Hb. We excluded seven patients: three with confounding co-morbidities (one each for superficial bladder cancer, polycythemia vera, and rectal cancer) and four due to missing baseline hematological parameters. Three other patients had Grade I/II rectal bleeding and one had Grade I/II hematuria, respectively. As these radiotherapy-related side effects were unlikely to have had a significant effect on the Hb or hematocrit, they were included in the analysis. Two patients died due to unrelated causes (esophageal cancer and cardiac failure). These patients were included in the study until the point of diagnosis of their co-morbid diseases. Median age of the 72 evaluable patients was 64.2 years at the time of radical prostatectomy. Median follow-up was 37 months as of March 2004. At the time of this report, none had recurrence of prostate cancer with their PSA remaining at an undetectable level (<0.2 ng/ml).

Figure 1 and 2 show the pattern of decline and recovery of mean Hb, hematocrit, and testosterone. In general, the pattern of change in mean Hb and hematocrit was closely parallel to that of testosterone. The mean Hb at baseline was 148.4 g/L (range: 122 - 170 g/L). At the second visit, which was after the completion of radiotherapy but just before the start of androgen suppression, mean Hb dropped to 146.2 g/L. This 2.2 g/L change was statistically significant decline from the baseline (p=0.03). The maximum Hb drop during the 2-year androgen suppression occurred at 24 months after the commencement of androgen suppression. Mean Hb declined by 10.5 g/L from the baseline to this nadir. During this interval, 49 out of 58 evaluable patients had a Hb decrease (range: 1-43 g/L). When measured from the start of androgen suppression to the nadir, mean Hb declined by 8.3 g/L, and 45/60 patients had a Hb decrease (range: 2-35 g/L). These declines in mean Hb were statistically significant (p<0.0001). The range of Hb decline from the baseline to various time points was depicted in Table 1.

The rate of Hb decline and recovery was not uniform. During the androgen suppression phase, Hb initially fell rapidly. This was followed by more gradual decline and then a plateau by 8 months. In the post-suppression phase, the recovery of Hb was initially gradual, but accelerated with more time. The

TABLE 1. **Range of Hb drop from baseline to various time points in follow-ups**

Hb decline (g/L)	Baseline to Post RT (n)	Baseline to Nadir during AS (n)	Post RT to Nadir during AS (n)
Not recorded	2	14	12
No decline	30	9	15
≤ 5	13	9	12
6 - 10	18	7	7
11- 15	7	14	11
16 – 20	1	14	9
21 – 25	1	2	3
> 25	0	3	3

n: number of patients, RT: radiotherapy, AS: androgen suppression

recovery of both Hb and testosterone to pretreatment levels appeared slow and might take up to 2 years, although more patients with longer follow-up are required to make an accurate assessment of the timing and extent of their recovery. Age did not affect the baseline Hb and testosterone levels, or the pattern of the decline and recovery of these parameters.

Mean platelet count declined slightly with radiotherapy (18 $X10^9$/L, p=0.03). MCV did not show any significant change with radiotherapy. During the suppression and post-suppression phase, there was no discernable pattern of change in both MCV and platelet count (data not shown).

Figure 3 shows the changes of the mean scores of the three domains, represented by 0 to ±100 scale, during the 2-year androgen suppression. A positive change in the Fatigue score means an increase in fatigue, while a negative change in the Global Health Status and Physical Functioning scores indicates a deterioration of these domains. The change in mean score about 5-10 is considered "little" change in the quality of life, while 10-20 and >20 change are regarded as "moderate" and 'very much" change, respectively.[2]

In order to assess a potential impact of Hb change on the quality of life, the scores for each of the three quality of life domains were correlated with Hb for each visit as well as for every patient individually. Table 2 describes Pearson correlation coefficients between the scores of the three domains and absolute Hb values at each visit and their corresponding p-values. At the baseline, Hb had a weak, but statistically significant, correlation with Fatigue, Global Health Status, and Physical Functioning. However, during the 2-year androgen suppression, there was no consistent correlation between Hb and the scores of the three domains. Nor was there a trend in the correlation coefficients in either positive or negative direction. These findings suggest that the magnitude of Hb change observed during the androgen suppression and post-androgen suppression phase was not significant enough to affect the three domains of quality of life. When the correlation between Hb and the scores of the three domains at each visit was analyzed for each individual patient (this data not shown), statistically significant correlation was present in less than 10% of patients.

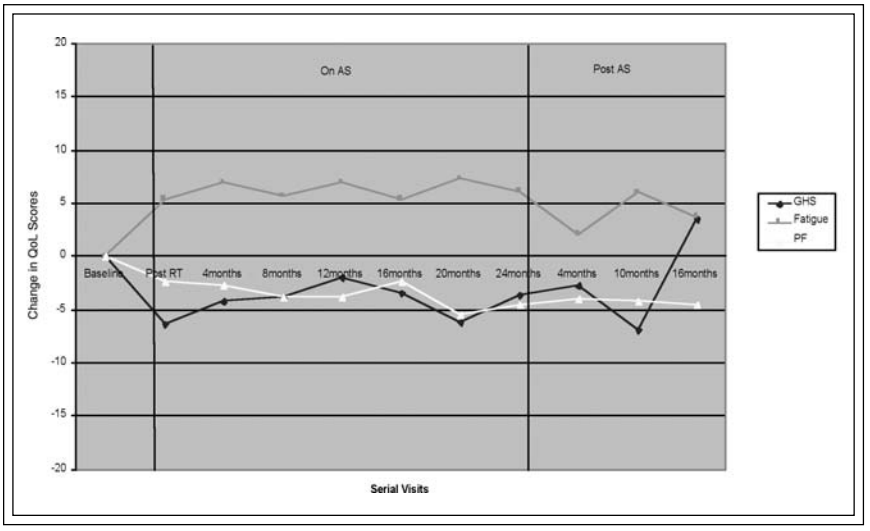

Figure 3. Change of the three quality of life parameters from baseline at serial follow-up visits. GHS: global health status, PF: physical functioning, QoL: quality of life, AS: androgen suppression.

Discussion

Suppression of androgens inherently carries a risk of anemia, since androgens have erythropoietic effect. Erythropoietic mechanism of androgens is well described by Molinari.[3] When androgens enter the erythrocytes, they are reduced to 17-keto derivatives by NADPH-dependant dehydrogenases. These 17-ketosteroids are then delivered to

TABLE 2. **Pearson correlation coefficients (r-values) between the three quality of life domains and absolute hemoglobin values at each visit, and corresponding p-values**

	Base-line	Post-RT	AS, 4 Mo.	AS, 8 Mo.	AS, 12 Mo.	AS, 16 Mo.	AS, 20 Mo.	AS, 24 Mo.	Post-AS, 4 Mo.	Post-AS, 10 Mo.	Post-AS, 16 Mo.
Fatigue	-0.24	-0.31	-0.11	-0.28	-0.19	-0.24	0.033	-0.06	0.10	-0.14	0.03
	p<0.05	p<0.01	p>0.2	p<0.02	p>0.1	p<0.05	p>0.2	p>0.2	p>0.2	p>0.2	p>0.2
PF	0.34	0.2	0.236	0.2	0.166	0.08	0.12	0.066	-0.17	0.21	0.28
	p<0.01	p>0.1	p<0.05	p>0.1	p>0.2	p>0.2	p>0.2	p>0.2	p>0.2	p>0.2	p>0.2
GHS	0.292	0.19	0.169	0.217	0.133	0.303	0.1	0.24	-0.02	0.134	0.08
	p<0.02	p>0.1	p>0.2	p>0.1	p>0.2	p<0.01	p>0.2	p>0.1	p>0.2	p>0.2	p>0.2

GHS: global health status, PF: physical functioning, AS: androgen suppression, RT: radiotherapy, Mo: months.

the bone marrow cells, which have specific testosterone receptors. They enhance the differentiation of uncommitted stem cells to erythroid committed elements by synthesis of new m-RNA in the bone marrow. This stimulatory effect is balanced by a negative feedback mechanism. There have been a few studies examining the effect of androgen suppression on Hb in prostate cancer patients.[4-6] Previous studies were limited by either the heterogeneity of study patients or a lack of long-term follow-up. Our study, unlike others, targeted a specific, well defined, non-metastatic group of prostate cancer patients that underwent a finite period of reversible androgen suppression using a GnRH analogue as monotherapy. Our series also attempted to evaluate the change of Hb over a long period of time and included the change of Hb during both androgen suppression and post-androgen suppression phase. Furthermore the potential effect of Hb change on the quality of life was examined with a correlation analysis.

In our study, the maximal drop of mean Hb from the baseline during the 2-year androgen suppression was 10.5 g/L. This extent of Hb decline is similar to that reported with orchiectomy. Hamilton[7] described the effect of involuntary bilateral orchiectomy in six healthy prisoners in 1948, and reported that orchiectomy resulted in a decrease of mean Hb by 10 g/L in 40 days and a fall of testosterone to castrate levels in 10 days. Fonesca[4] also reported in a cohort of 64 patients with metastatic prostate cancer that bilateral orchiectomy led to a median decrease of Hb by 12 g/L within 90 days of surgery.

Our study used a GnRH analogue alone (i.e. monotherapy) for the suppression of androgen except in the initial phase during which an anti-androgen was added for only 4 weeks to block the effect of a potential flare-up of testosterone caused by the initiation of a GnRH analogue. Others reported a greater Hb decline when complete androgen suppression consisting of a GnRH analogue plus anti-androgen was used. Asbell[5] reported in a series of 141 prostate cancer patients that the combination of gosereline acetate plus flutamide resulted in a decrease of Hb by 28 g/L at 4 months after their commencement. Similarly, Strum[6] observed a 25g/L decline at 5.6 months after the initiation of complete androgen suppression in 133 prostate cancer patients. This difference in the magnitude of Hb decline between mono-therapy (using orchiectomy or GnRH analogue alone) and complete androgen suppression is likely due to the fact that orchiectomy and GnRH alone do not block the effect of adrenal androgens on erythropoiesis. Molinari[3] suggested that a small but constant amount of androgen (such as adrenal androgens) would be sufficient enough to stimulate the erythropoietic process.

The decline and recovery of mean Hb was closely parallel to that of testosterone, as shown in Figure 1. During the androgen suppression phase, mean Hb declined with the fall of testosterone, and remained at a subdued level in the presence of a castrated level of testosterone. In the post-androgen suppression phase, the recovery of Hb followed that of testosterone. This close association confirms the erythropoietic effect of testosterone. In our study where GnRH analogue was administered for 2 years, the time required for the recovery of testosterone and Hb to the pretreatment levels appeared close to 2 years. In other studies where GnRH analogues were used to treat benign prostatic hypertrophy for 6 months or so, the recovery period for testosterone and Hb was 6 months.[8,9] These observations suggest that the length of androgen suppression is a major factor in determining the recovery timing of testosterone and Hb after discontinuing GnRH analogues.

How are hemoglobin levels affected by androgen deprivation in non-metastatic prostate cancer patients?

In most of our cohorts, Hb decline during the 2-year androgen suppression was less than 20 g/L, as shown in Table 1. Only 5/58 and 6/60 had Hb decline > 20 g/L from the baseline to the nadir and from the post-RT to the nadir, respectively. Thus, it appears reasonable to recommend no additional investigations for Hb decline, when Hb drop is < 20g/L during androgen suppression, provided that androgen suppression is achieved by either orchiectomy or GnRH analogue alone. This general guideline can be useful for clinicians providing medical care for this group of patients, as it would help patients and clinicians avoid unnecessary anxiety or costly investigations for Hb decline. Investigations may be limited to only those with Hb decline > 20 g/L while on androgen suppression, or failure of Hb recovery to a pre-treatment level in spite of the complete recovery of testosterone after the cessation of androgen suppression.

The important question to address is the clinical significance of Hb decline secondary to androgen suppression. However this is very difficult to answer because of other confounding factors. Testosterone is an anabolic hormone, and is responsible for maintaining the energy levels and libido in men. Lowering testosterone levels is known to reduce libido, muscle mass and energy levels amongst other effects. Thus, it is difficult to determine how much of an effect the reduction in Hb itself has on the change in quality of life. Nevertheless we postulated that Fatigue, Physical Functioning, and Global Health Status in the questionnaire would be the relevant domains that would be affected, if the drop in Hb was producing a clinical effect. In our study, there was "little" to "no change" in Global Health Status, Physical Functioning and Fatigue at the end of 2-year androgen suppression. Very few patients showed significant correlation of these domains with Hb levels. Also, the correlation did not grow stronger or retain significance throughout the androgen suppression phase. Thus it appears in our study that the magnitude of Hb drop brought on by androgen suppression did not result in any significant adverse effect on the three domains of the quality of life.

In conclusion, Hb declined by 10.5 g/L during a 2-year course of androgen suppression. The pattern of the decline and recovery of Hb was similar to that of testosterone. The extent of Hb decline observed during the 2-year androgen suppression did not appear to result in any adverse effect on the general functioning of a patient. □

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