Int. J. Radiation Oncology Biol. Phys., Vol. 62, No. 3, pp. 719–724, 2005

0360-3016/05/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2004.11.008

CLINICAL INVESTIGATION **Prostate**

EFFECT OF ANDROGEN SUPPRESSION ON HEMOGLOBIN IN PROSTATE CANCER PATIENTS UNDERGOING SALVAGE RADIOTHERAPY PLUS 2-YEAR BUSERELIN ACETATE FOR RISING PSA AFTER SURGERY

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Purpose: To examine the effect of 2-year androgen suppression (AS) on the pattern and extent of hemoglobin (Hb) change.

Methods and Materials: The basis of this report was a Phase II study evaluating a combined treatment of salvage radiotherapy plus 2-year AS for a rising prostate-specific antigen level after surgery. Patients had laboratory tests performed, including Hb and serum testosterone, and answered a quality-of-life questionnaire (European Organization for Research and Treatment of Cancer Quality-of-life Questionnaire 30 item) at regular intervals during the AS and post-AS period. The pattern and extent of the change in Hb was analyzed in relation to the testosterone level. The clinical significance of the Hb change was evaluated with a correlation analysis between Hb and the three specific domains of the questionnaire (Global Health Status, Physical Functioning, and Fatigue).

Results: Of a total of 74 accrued patients, 69 were identified as eligible for this report. The median patient age was 70 years. The median follow-up was 38.6 months. The mean Hb was 150.7 g/L at baseline and declined with radiotherapy by 5.9 g/L. The maximal Hb drop during AS was 16.0 g/L ($p < 0.0001$), occurring at 16 months after the initiation of AS. Hb recovery in the post-AS period was slow. The decline and recovery of the mean Hb and hematocrit followed that of testosterone. The three quality-of-life domains did not show any significant correlation with the change in Hb.

Conclusion: Two-year AS resulted in a statistically significant drop in the mean Hb, but had no clinically apparent adverse effect. The pattern of Hb change was similar to that of testosterone change.

Prostate cancer, Erythropoiesis, LHRH agonists, Hemoglobin, Androgen suppression.

INTRODUCTION

Androgen suppression (AS) has been increasingly used for the management of prostate cancer in recent years. In addition to its traditional role in the management of metastatic disease, its indication has been expanded to the adjuvant and/or neoadjuvant setting. Because patients receiving AS as an adjuvant to definitive therapy are usually long-term survivors, it is important to evaluate the potential adverse effects of prolonged AS.

The erythropoietic effect of androgens has been known for the past half century or more (1, 2). Androgens have been used to treat anemia due to chronic disease such as aplastic anemia (3) and renal failure (4). Molinari (5) described the erythropoietic mechanism of androgens in his detailed review of the subject. No difference in serum erythropoietin levels is apparent between normal men and women, even though the difference in their respective hemoglobin (Hb) levels is significant (6, 7). Several studies have suggested that the physiologic level of testosterone in men is responsible for this gender difference in Hb level (8–11). Thus, any therapeutic maneuver leading to AS carries a potential risk of anemia.

The aim of this report was to examine the pattern and extent of Hb change in prostate cancer patients undergoing a combined approach of salvage radiotherapy (RT) plus

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Supported in part by educational grant from Aventis Pharma Inc.

Acknowledgments—We thank Brian Kong, B.A. and Inna Barak, C.C.R.A. for data management assistance.

Received June 9, 2004, and in revised form Oct 22, 2004. Accepted for publication Nov 1, 2004.

2-year AS for prostate-specific antigen (PSA) relapse after radical prostatectomy.

METHODS AND MATERIALS

The group of patients we examined for this report were from a Phase II study evaluating the efficacy of a combined approach of salvage RT plus 2-year AS for prostate cancer patients with PSA relapse after radical prostatectomy. PSA relapse after surgery was defined as a PSA level >0.2 ng/mL, with two or more consecutive PSA increases during a minimum of 6 months. The local research ethics committee approved the study, and it was open for accrual between 1998 and 2002.

All the patients were treated with salvage RT to the prostate bed plus 2 years of AS. The radiation dose and fractionation schedule was 6600 cGy in 33 fractions within 6.5 weeks. RT was delivered with a four-field technique and 18-MV photons. The target volume of RT was limited to the prostatic bed and periprostatic tissue, and no attempt was made to treat the regional pelvic lymph nodes. The radiation field sizes ranged from $8 \times 8 \times 8$ cm to $11 \times 11 \times 10$ cm. AS was started within 2 weeks after completion of RT. It consisted of oral nilutamide 100 mg three times daily for 4 weeks and subcutaneous buserelin acetate 6.3 mg depot every 2 months for 2 years. Nilutamide was given 1–2 weeks before the first injection of buserelin acetate depot. Buserelin acetate is a synthetic peptide analog of gonadotrophin-releasing hormone, similar to leuprolide acetate or goserelin acetate. Chronic administration of buserelin acetate ensures continuous suppression of testosterone secretion.

The baseline laboratory investigations before the therapeutic intervention included complete blood count, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, prostate-specific antigen, and testosterone. These tests were repeated 2–4 weeks after the completion of RT (just before the initiation of buserelin acetate), and then every 4 months during the 2 years of AS, and every 6 months thereafter. The parameters we analyzed for this report were hemoglobin (Hb), hematocrit, mean cell volume (MCV) of erythrocyte, platelet, and testosterone levels. We carefully examined the patient records to determine whether any comorbidity or medical event was present or had occurred that could have influenced the baseline or subsequent Hb levels. Preexisting medical conditions, surgical interventions, or posttreatment complications such as rectal and/or urethral bleeding were recorded, and their nature and severity were assessed. When a patient was judged to have a confounding factor significantly affecting Hb level for the long term, he was excluded from the analysis. However, when the confounding event was temporary, affecting only the laboratory results at the time of the event (e.g., knee arthroplasty), we excluded only those affected results and kept the patient and his remaining data for analysis. For patients who received <12 injections of buserelin acetate (8 patients), the entire laboratory results up to the date of the last buserelin injection were included for analysis.

Quality-of-life parameters were also collected with a questionnaire (European Organization for Research and Treatment of Cancer quality-of-life questionnaire 30-item, version 3.0) at each visit. To assess the impact of Hb change on the quality of life, we examined the changes in the scores of the three specific domains of this 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 article and will be reported separately.

Statistical Analysis

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

RESULTS

The study was closed in April 2002 and had accrued a total of 74 patients. For the analysis of the effect of 2 years of AS on Hb, 69 patients were identified as eligible. Five patients were excluded: 1 each for bladder cancer, sickle cell anemia, and gastrointestinal stromal tumor and 2 with persistent and heavy RT-related rectal bleeding. Four patients each had Grade I-II rectal bleeding and Grade I-II hematuria respectively. However, because these RT-related side effects did not appear to have a significant effect on Hb or hematocrit at any time, these patients were included in this study. At the last follow-up, only 1 patient had had biochemical relapse with a rising PSA level. This patient was also included in the analysis up to the time of additional hormonal manipulation with the addition of Casodex. None had received Epoetin Alfa for a low Hb. The median age of the 69 assessable patients was 70 years at salvage RT. The median interval from radical prostatectomy to salvage RT was 3.5 years. The median follow-up time was 38.6 months as of March 2004.

Figures 1 and 2 show the patterns of decline and recovery of the mean Hb, hematocrit, and testosterone. The mean Hb at baseline was 150.7 g/L (range, 109–181 g/L). At the second visit, which was after RT completion and just before the start of AS, the mean Hb had dropped to 144.8 g/L, a statistically significant decrease from baseline ($p < 0.001$). RT appears to have resulted in a mean drop of 5.9 g/L. Of 63 assessable patients, 45 had a Hb drop ranging from 1 to 29 g/L after RT. During the 2 years of AS, the Hb nadir drop occurred at 16 months after beginning AS. The drop in mean Hb to the nadir was 16.0 g/L from baseline and 10.1 g/L from the post-RT reading, both of which were statistically significant declines ($p < 0.0001$). Of the 62 patients, 61 and 50 recorded a Hb decline from baseline to nadir (range, 3–48 g/L) and from the post-RT value to the nadir (range, 0–24 g/L), respectively. The decline in Hb was not uniform throughout the AS phase. The Hb drop was greater at the start of AS than during the subsequent period of AS. The Hb drop was 5.1 g/L during the first 4 months of AS compared with 1.5, 1.3, and 2.0 g/L during the subsequent 4-month intervals.

The pattern of change in the mean Hb and hematocrit was

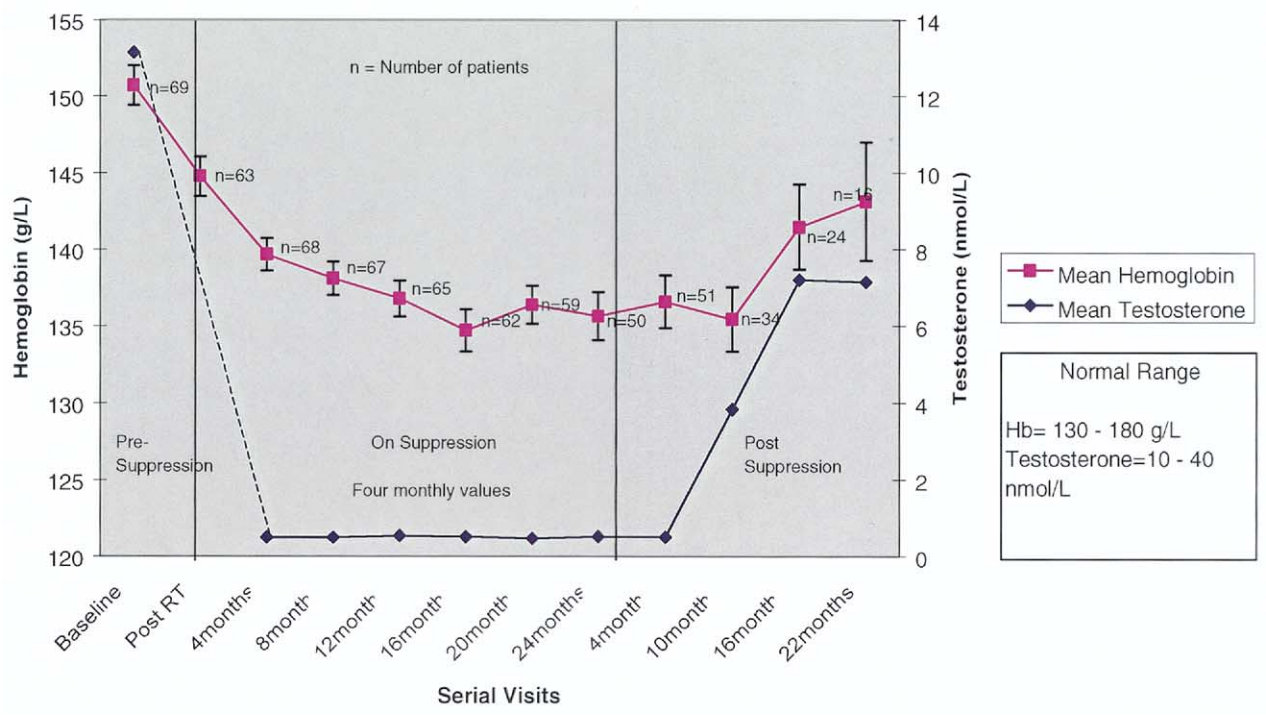

Fig. 1. Variation in mean hemoglobin (Hb) with standard error bars and mean testosterone at serial follow-up visits. Follow-up intervals vary along x-axis as depicted.

very similar to that of the testosterone level. The initial phase of rapid fall, followed by a gradual decline in Hb and hematocrit was to some extent similar to the pattern of change of testosterone, which decreased rapidly initially with the start of AS and then remained at the castrate level during the subsequent period. The rise in Hb and hematocrit in the postsuppression phase also followed the pattern of testosterone recovery. The number of patients in the post-suppression phase was small, resulting in wider standard error bars (Fig. 1) and limited evaluation of the pattern of change. However, as shown in Fig. 1, the recovery of both Hb and testosterone to pretreatment levels was slow and could take up to ≥2 years.

A gradual drop occurred in the mean MCV throughout

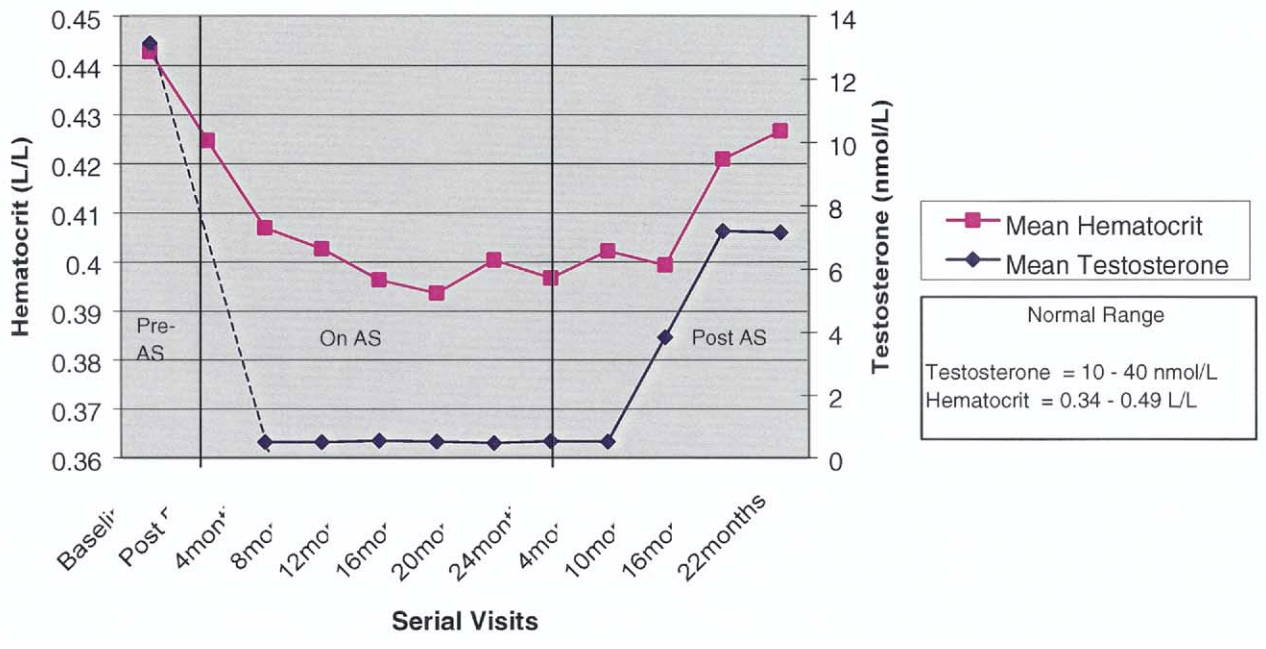

Fig. 2. Variation in mean hematocrit and mean testosterone at serial follow-up visits. AS = androgen suppression.

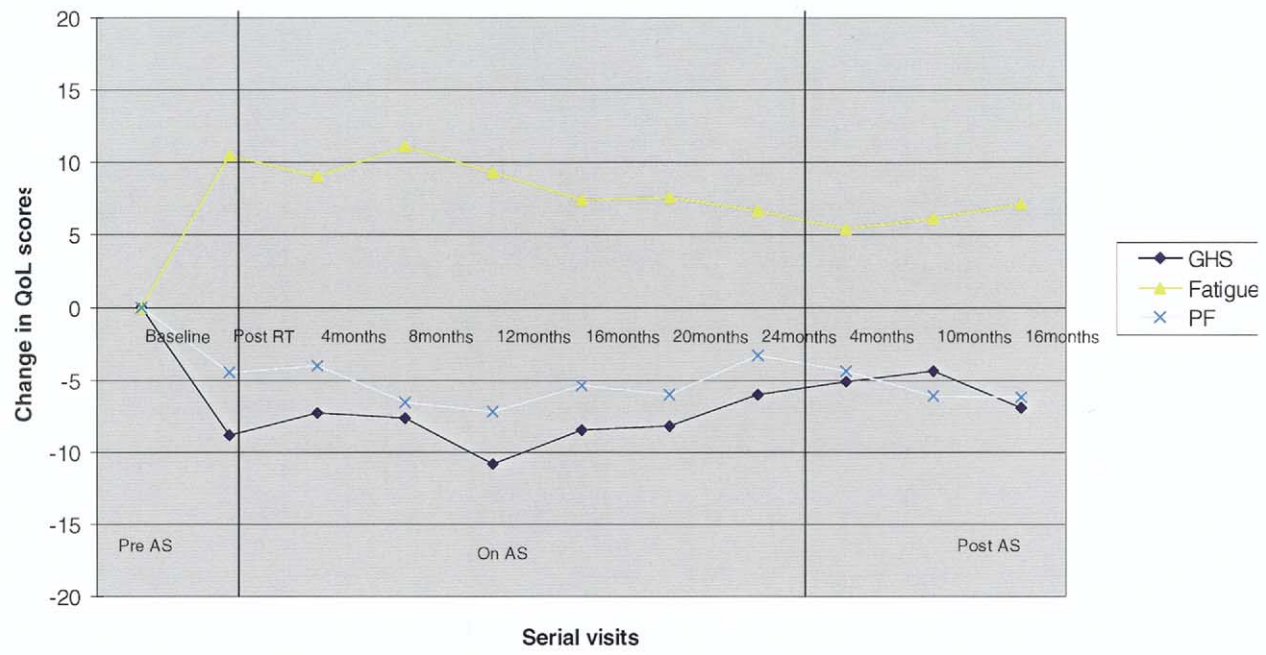

Fig. 3. Change in quality-of-life parameters from baseline at serial follow-up visits. GHS = Global Health Status; PF = Physical Functioning; QoL = quality of life.

the AS phase, followed by a rapid recovery in the postsuppression phase. The maximal drop in the mean MCV from baseline was only 1.1 fL (statistically significant, $p = 0.0007$), occurring 24 months after beginning AS. The mean platelet count declined by 11×10^9/L with RT; this, however, was not statistically significant ($p = 0.2$). The mean platelet count did not show any significant change or particular pattern during the AS and postsuppression phase.

Quality of life

Figure 3 shows the changes in the mean scores of the three domains, represented by 0 to 100 scale, during the 2 years of AS. A change in the mean score of about 5–10 is considered a "little" change in the quality of life and 10–20 and >20 change as "moderate" and "very much" change, respectively (13).

To assess for any correlation between the change in Hb and the change in the three domains, the scores for each of the three domains were correlated with Hb for each visit, as well as for every patient individually. Table 1 describes Pearson correlation coefficients between the scores of these three domains and absolute Hb values at each visit and their corresponding p values. At baseline, Hb had a weak, but statistically significant, positive correlation with Global Health Status and Physical Functioning. It did not, however, show a significant correlation with Fatigue. During the 2 years of AS, no consistent correlation was found between Hb and the scores of the three domains. Nor was a trend found in the correlation coefficients in either the positive or negative direction. These findings suggest that the magnitude of Hb change observed during the AS 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 (data not shown), only 1, 8, and 3 patients showed a statistically significant correlation of Hb with Fatigue, Global Health Status, and Physical Functioning, respectively.

DISCUSSION

A statistically significant decline was observed in Hb during the 2 years of AS in our study. Our data suggested that AS was a major contributory factor for Hb decline, although both RT and AS played a role in the Hb drop. The maximal drop in the mean Hb from baseline was 16.0 g/L, occurring about 16 months after beginning AS. This magnitude in Hb decline was similar to that reported with orchiectomy. Hamilton (14), describing the effect of involuntary bilateral orchiectomy in 6 healthy prisoners, reported in 1948 that the mean Hb fell by 10 g/L in 40 days and testosterone fell to castrate levels in 10 days. In another study by Fonseca *et al.* (11), bilateral orchiectomy resulted in a median decrease in Hb by 12 g/L within 90 days of surgery in 64 patients with metastatic prostate cancer.

Other studies have reported a greater Hb decline when complete androgen blockade, consisting of a luteinizing hormone-releasing hormone (LHRH) analog and a nonsteroidal antiandrogen, was used. Asbell *et al.* (10) reported that Hb decreased by 28 g/L at 4 months after the start of goserelin acetate plus flutamide. Similarly, Strum *et al.* (12) observed a 25 g/L decline at 5.6 months after the initiation of complete androgen blockade. This difference in the magnitude of Hb decline between monotherapy (using orchiec-

Table 1. Pearson correlation coefficients (r) between three quality-of-life domains and absolute hemoglobin values at each visit and corresponding p value

			During androgen suppression (mo)						After androgen suppression (mo)		
Domain	Baseline	After RT	4	8	12	16	20	24	4	10	16
Fatigue	−0.16 (>0.1)	−0.07 (>0.2)	0.06 (>0.2)	−0.03 (>0.2)	0.09 (>0.2)	−0.01 (>0.2)	−0.21 (>0.1)	−0.01 (>0.2)	0.06 (>0.2)	−0.07 (>0.2)	−0.09 (>0.2)
GHS	0.26 (<0.002)	0.03 (>0.2)	0.11 (>0.1)	0.19 (>0.05)	−0.05 (>0.2)	0.01 (>0.2)	0.36 (>0.2)	0.05 (>0.2)	0.15 (>0.2)	0.13 (>0.2)	0.35 (>0.1)
PF	0.29 (<0.05)	−0.0006 (>0.2)	0.16 (>0.2)	0.23 (>0.1)	−0.04 (>0.2)	0.11 (>0.2)	0.18 (<0.01)	0.07 (>0.2)	0.09 (>0.2)	−0.05 (>0.2)	0.37 (>0.1)

Abbreviations: GHS = Global Health Status; PF = Physical Functioning, RT = radiotherapy.
Data in parentheses are p values.

tomy or luteinizing hormone-releasing hormone analog alone) and complete androgen blockade is likely because orchiectomy or LHRH alone does not block the effect of adrenal androgens on erythropoiesis. Molinari (5) suggested that a small, but constant, amount of androgen would be sufficient enough to stimulate the erythropoietic process.

The decline in Hb was not uniform throughout the AS phase in our study. The Hb drop was greater in the beginning of AS than during the subsequent period. This may have been a reflection of either a more rapid fall in serum testosterone at the beginning of AS or the effect of complete androgen blockage brought on by the nilutamide that was used for 4 weeks at the beginning of AS.

On the basis of our preliminary data, the recovery of Hb seemed slow and might take up to ≥2 years after the cessation of AS. This slow recovery of Hb appears directly related to the slow recovery of testosterone (to the pretreatment level) in the postsuppression phase. In our study, it took at least 16 months for testosterone to achieve a meaningful recovery, and it had not return to the pretreatment level by 22 months after the discontinuation of AS. Another potential factor contributing to a slow recovery of testosterone is the direct effect of radiation on the testicular production of testosterone. However, Pickles *et al.* (16) reported that a radiation-related testosterone decline typically resolved by 18 months after RT. Thus, it is very unlikely that the direct effect of radiation on testicular production of testosterone played a major role for the sustained testosterone suppression beyond 24 months after RT in our cohort. Strum *et al.* (12) reported a similar, prolonged, AS in the postsuppression phase after 12 months of combined androgen blockade. The pathophysiologic mechanism for this slow recovery of testosterone in the postsuppression phase has been, in recent years, the subject of additional investigation (15). In other studies in which LHRH analogs were used for the management of benign prostatic hyperplasia for a shorter duration (around 6 months), the recovery period for Hb and testosterone was 6 months (8, 9). These studies and our data suggest that the length of AS dictates the time to recovery for testosterone and Hb.

The important question to address is the clinical significance of Hb decline secondary to AS. 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 the testosterone levels is known to reduce libido, muscle mass, and energy levels, among 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, "little" to "no change" in Global Health Status, Physical Functioning, and Fatigue was observed at the end of 2 years of AS. Very few patients showed a significant correlation of these domains with the Hb levels. The correlation did not grow stronger or

retain significance throughout the AS phase. Thus, it appears, in our study, that the magnitude of Hb drop brought on by AS did not result in any significant adverse effect on the three domains of the quality-of-life questionnaire.

Our series is unique in several aspects compared with other published studies evaluating the effect of AS on Hb. First, our study examined the effect of AS on Hb for a much longer period. All previous studies reported the change in Hb during the first 6–12 months after beginning AS. In contrast, our series examined the pattern of change of Hb during a minimum of 2 years. Second, our study targeted a specific, well-defined, nonmetastatic group of prostate cancer patients who underwent a finite period of reversible AS using a LHRH analog as monotherapy. The classes of patients assessed in other published studies were those that underwent short-term reversible AS for benign prostatic hyperplasia (8, 9), combined androgen blockade (10, 12), or orchiectomy. Third, our series attempted to assess the recovery of Hb in the postsuppression phase, as well as the pattern of Hb decline during the AS phase.

CONCLUSION

A statistically significant decline in Hb was observed during a 2-year course of AS, and its maximal drop occurred at 16 months after the beginning of AS. The pattern of the decline and recovery of Hb was similar to that of testosterone. The extent of Hb decline observed during the 2 years of AS did not appear to result in any adverse effect on the general functioning of a patient.

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