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REVIEW

Hematological changes during androgen deprivation therapy

Mathis Grossmann and Jeffrey D Zajac

Androgen deprivation therapy (ADT) has been associated with a plethora of adverse effects, consistent with the androgen dependency of multiple reproductive and somatic tissues. One such tissue is the hemopoietic system, and one of the most predictable consequences of ADT is the development of anemia. Although anemia caused by ADT is rarely severe, ADT is often given to frail, elderly men with increased susceptibility to anemia due to multiple other causes. ADT-associated anemia may contribute to fatigue and reduced quality of life (QoL) in such men, although this requires further study. While anemia is an independent risk factor of mortality in men with prostate cancer, it is not known whether treatment of ADT-associated anemia alters clinically important outcomes, or whether treatment affects mortality. Awareness of the phenomenon of ADT-induced anemia should avoid unnecessary work-up in mild cases of normocytic normochromic anemia. However, assessment and treatment of more severe anemia may be required. This should be determined on an individual basis. In contrast to the well-described actions of ADT on erythropoiesis, its effect on other hemopoietic lineages has been less well elucidated. While preclinical studies have found roles for androgens in maturation and differentiated function of neutrophils, lymphocytes and platelets, the implications of these findings for men with prostate cancer receiving ADT require further studies.
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INTRODUCTION

Prostate cancer is the most common non-skin cancer in men, with a lifetime risk of one in nine, and the incidence is rising due to more frequent prostate-specific antigen (PSA) testing.[1] Use of androgen deprivation therapy (ADT) has increased markedly in the USA, where one-third of the two million prostate cancer survivors are receiving this treatment.[2] Similarly in Australia, the use of ADT from 2003 to 2009 has increased by more than 40%.[3] Thus, ADT, which intentionally reduces serum testosterone levels to castrate range (<5% of the normal value), and serum estradiol levels to <30%,[4] has become the most common contemporary cause of severe male hypogonadism. While ADT is established therapy for metastatic prostate cancer, most of the recent increase in ADT use has occurred in men with organ-confined or low volume metastatic prostate cancer, or with biochemical PSA recurrence. Since such men have excellent rates of cancer-specific survival (up to 90%), the benefits of ADT need to be carefully balanced against the toxicities, which are a direct consequence of the induced hypogonadism.[1]

Adverse effects of ADT include firstly, loss of bone mineral density leading to fractures; secondly, weight gain, insulin resistance and diabetes;[5–7] thirdly, sexual symptoms such as sexual dysfunction, gynecomastia, decrease in testicular and penile size, loss of sexual hair; and, fourthly, general and constitutional symptoms including neurophysiological symptoms (reduced mood cognition, quality of life (QoL)), hot flushes, fatigue and anemia.[1,8]

Given that prostate cancer is a disease predominantly of ageing men, age itself and associated comorbidities may contribute to increased vulnerability of the hemopoietic system to ADT, although this assumption has not been formally tested in clinical studies. Indeed, older men may have pre-existing anemia, before commencement of ADT from multiple causes, which may require appropriate investigation and treatment as dictated by the clinical scenario.

In this review, we will focus on hematological consequences of ADT, and will discuss the effects of androgens, and of androgen withdrawal, on the red blood cell lineage. Effects of androgens on other hemopoietic lineages, such as white blood cells, and platelets are less well described and will be summarized briefly.

METHODOLOGY

The clinical and experimental studies discussed in this review were retrieved from the peer-reviewed journals indexed on the PubMed database from January 1954 to June 2011. Multiple searches were performed, using the search terms testosterone, androgen, erythropoiesis, polycythemia, hemopoiesis, white cell, lymhocyte, neutrophil, thrombocyte, platelet, prostate cancer and males. Historical references (published prior to 1954) were retrieved from library archives.

ANDROGENS AND ERYTHROPOIESIS: CLINICAL STUDIES

Stimulation of erythropoiesis by androgens

Stimulatory effects of androgens on erythropoiesis have been demonstrated in animal experiments since the 1940s, when it was shown that castration of male rats led to a marked decrease in erythropoietic activity, and that this decrease in red blood count could be rescued by the administration of androgens.[9] The interested reader is referred to an excellent review[10] on this topic by the group of Dr Basaria, guest editor of this special section of the *Asian Journal of Andrology*. Such early animal experiments provided an explanation for the observation that adult men have higher red blood counts and hemoglobin levels (about 1–2 g dl^{-1}) than adult women. Consistent with a stimulatory action of androgens on erythropoiesis, hemoglobin levels are similar

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in prepubertal boys and girls but rise during male puberty, mirroring the increase in testosterone levels.[10] The alternate explanation that the lower hemoglobin in postpubertal women is due to menstruation-induced iron deficiency was refuted by multiple lines of evidence, including early observations that women with surgical menopause still have lower hemoglobin levels than men.[11] Indeed, it was recognized that androgens can stimulate erythropoiesis in women, evidenced by increased red cell mass in women with androgen excess.[10] For example, we have recently encountered a case of a karyotypically female (XX) with congenital adrenal hyperplasia, who, due to non-compliance with glucocorticoid therapy, presented with heavy virilization and severe polycythemia leading to a thrombotic stroke.[12]

Androgen deficiency and anemia

Anemia in men with classical hypogonadism. Consistent with a stimulatory effect of androgens on erythropoiesis, men with untreated hypogonadism commonly have mild anemia, which responds to testosterone replacement therapy. In one prospective study, of hypogonadal men (mean serum total testosterone level of 2.7 nmol l^{-1} at baseline) receiving testosterone therapy, hematocrit increased markedly, from mildly anemic (38.0%±3.0%) to mid-normal (43.1%±4.0%; $P=0.002$) within 3 months, and remained at that level for the duration of treatment.[13] In a retrospective analysis of 100 men with pituitary adenomas, 46% were anemic and the average hematocrit was 39.9% in men with low testosterone, compared to 45.6% in men with normal testosterone ($P<0.001$). Anemia remained associated with low testosterone after adjusting for pituitary tumor size (odds ratio (OR): 19; 95% CI: 4.9–77), and men receiving testosterone therapy had significantly higher hematocrit values compared to untreated men with low testosterone.[14]

Testosterone and anemia in men with diabetes. Interestingly, in addition to anemia associated with classical hypogonadism due to testicular or pituitary pathology, even less pronounced reductions of serum testosterone levels contribute to anemia. In a cross-sectional study of 464 men with diabetes, men with a total testosterone level of <10 nmol l^{-1} were more likely to have anemia (adjusted OR: 1.7; 95% CI: 1.1–2.8) than men with a total testosterone level of >10 nmol l^{-1}.[15] Similarly, anemia was twice as common in those with a calculated free testosterone of <230 pmol l^{-1} (adjusted OR: 2.0; 95% CI: 1.2–3.1). The overall prevalence of anemia was 24% in this population, and was relatively mild, with the mean hemoglobin 12.1±0.1 g dl^{-1} in the 108 men with anemia compared to 14.9±0.1 g dl^{-1} in the 356 non-anemic men. Testosterone levels remained associated with anemia independent of confounders such as age, renal function, systemic inflammation and iron stores, and determined a remarkable 6%–8% of the total variability in hemoglobin levels.[15] These findings that testosterone deficiency may contribute to an increased frequency of anemia in men with diabetes, confirmed elsewhere,[16] are important not only because of the high prevalence of low testosterone levels in men with diabetes,[17] but also because of the overlapping symptomatology of hypogonadism with anemia.[18] Whether diabetic men presenting with anemia should be screened for testosterone deficiency and *vice versa* deserves further study.[19,20]

Age-related anemia in the general population. In addition to men with diabetes, low testosterone also increases the risk of anemia in older men, and women, in the general population. In a prospective study of 905 persons from the InCHIANTI cohort living in Tuscany, Italy, testosterone levels were associated with hemoglobin levels at baseline, and men and women with low testosterone levels had, independent of confounders, a significantly higher risk of developing anemia at a 3-year follow-up, relative risk 2.1 (95% CI: 1.1–4.1) for total and 2.9 (95% CI: 1.7–7.8) for bioavailable testosterone.[21] Similarly, in a cross-sectional analysis of 492 Australian men aged 30–94 years from the Busselton Health Survey, total testosterone was associated with hemoglobin ($P=0.003$) as was free testosterone ($P<0.001$), independent of confounders, suggesting that testosterone concentration modulates hemoglobin levels in community-dwelling men across a wide age range.[22]

Androgen therapy and polycythemia

Consistent with the inverse relationship of testosterone levels and hemoglobin, polycythemia, or erythrocytosis is one of the most common and consistent adverse effects of testosterone therapy, and not infrequently dose-limiting, especially in older men. In an experimental testosterone dose–response study of men rendered hypogonadal with gonadotropin-releasing hormone agonists receiving graded doses of testosterone add-back, hemoglobin and hematocrit increased significantly in a linear, dose-dependent fashion, and increases were significantly greater in older compared to younger men.[23]

In a meta-analysis of 19 studies by Calof *et al.*,[24] which included 651 men with low or low normal testosterone levels treated with testosterone and 433 with placebo, an increase in the hematocrit was the most frequent adverse event associated with testosterone replacement, and testosterone-treated men were nearly four times as likely to have hematocrit >50% as placebo-treated men (OR: 3.69, 95% CI: 1.82–7.51). This was confirmed in a more recent systematic review and meta-analysis of 51 studies of testosterone therapy, where testosterone treatment was associated with a significant increase in hemoglobin (weighted mean difference: 0.80 g dl^{-1}; 95% CI: 0.45–1.14) and hematocrit (weighted mean difference: 3.18%; 95% CI: 1.35 to 5.01).[25] Of the 35 men with a hematocrit of >50% in Calof's meta-analysis,[24] one patient had a cerebral hemorrhage. Indeed, a higher hematocrit is associated with increased blood viscosity and blood flow, increased risk of myocardial infarctions and cardiac death, and stroke.[26]

Therefore, the recently updated US Endocrine Society clinical practice guidelines on testosterone therapy in men with androgen deficiency syndromes recommend careful monitoring of hematocrit and hemoglobin during testosterone treatment.[19] Predictors of testosterone therapy-associated polycythemia include older age,[23] and the relative time blood testosterone concentrations remain in the supraphysiological range.[27] Polycythemia is also one of the most predictable consequence of androgen abuse or 'doping' in athletes, and likely contributes to the premature cardiovascular mortality associated with anabolic androgenic steroid abuse (for review, see Basaria).[28] A recent study by Basaria *et al.*[29] in a select group of older men with poor mobility found that testosterone therapy increased cardiovascular events, but numbers were small and the result may have been due to chance alone, given that a similarly designed study[30] has not confirmed this (see Ref. 31 for review). While men assigned to the testosterone group had a greater increase of hemoglobin and hematocrit than men assigned to placebo in Basaria's trial,[29] the observed increased risk of cardiovascular-related adverse events persisted even after adjustment for hematocrit levels.

The erythropoietic actions of androgens have also been exploited therapeutically in various forms of anemia, including, prior to the advent of recombinant erythropoietin, anemia of renal failure, aplastic anemia and the myelodysplastic syndrome.[10]

ANDROGENS AND ERYTHROPOIESIS: MECHANISMS

The exact mechanisms by which androgens regulate erythropoiesis have not been fully elucidated,[10,32] but there is evidence for both a direct stimulatory action on bone marrow erythroid progenitor cells *via* the

androgen receptor[33] as well as for indirect mechanisms involving erythropoietin[10] and the master iron regulatory protein hepcidin.[34] Currently available data on the relationship of androgens and erythropoietin, the key regulator of erythropoiesis, are contradictory. While earlier animal and human studies have shown that androgens increase the synthesis and secretion of erythropoietin,[10] a more recent prospective study showed that while testosterone dose-dependently increased hemoglobin and hematocrit levels in chemically castrated men, there was no associated increase in erythropoietin.[23] In addition, in population-based studies of men with[15,16] and without diabetes,[21] low testosterone remained a risk factor for anemia independent of erythropoietin levels. Consistent with the notion that hemopoietic actions of androgens are erythropoietin-independent are findings from studies in men undergoing hemodialysis, which found that concurrent androgen therapy not only augmented the anti-anemic effects of erythropoietin, but also reduced the erythropoietin dose necessary to maintain the target hemoglobin level.[35] Recently, it has been reported by Bhasin's group that testosterone therapy was associated with a dose-dependent suppression of serum hepcidin levels, and early changes in hepcidin predicted subsequent changes in hemoglobin and hematocrit.[34] Given that increased hepcidin, *via* regulation of the iron channel ferroportin, restricts systemic iron availability resulting in mild anemia, it is conceivable that testosterone-associated suppression of hepcidin, *via* increased iron availability, contributes to testosterone-induced erythropoiesis.[34] Although inflammation contributes to anemia, in a cross-sectional study of men with prostate cancer receiving ADT for at least 12 months, levels of circulating pro-inflammatory cytokines were not increased compared to eugonadal men not receiving ADT. As the authors of this study suggest, prospective studies are required whether initiation of ADT leads to acute changes in cytokine levels that may contribute to development of anemia.[36] The observation that testosterone, but not estradiol treatment stimulates erythropoiesis in aromatase-deficient men suggests that this pro-erythropoietic effect is a direct effect of androgen actiion which does not require aromatisation to estradiol.[37]

EFFECTS OF ADT ON ERYTHROPOIESIS

In light of the stimulatory effects of androgens on erythropoiesis, it is not surprising that androgen deprivation, either by surgical or medical castration, leads to anemia (**Table 1**). This phenomenon was first described in humans in 1948, when Hamilton[38] reported a series of six involuntarily castrated male prisoners with a mean decline in hemoglobin levels of 1 g dl^{-1} after 40 days. In a cohort of 64 men with prostate cancer from the Mayo Clinic, Minnesota, USA, who had no other cause for anemia, the median decrease of the hemoglobin level after bilateral orchiectomy was 1.2 g dl^{-1}. While the hemoglobin value fell below the normal range in 58%, only one patient had a hemoglobin level <9 g d^{-1}.[39] Combined androgen blockade (CAB), however, has been shown to cause a more substantial reduction in erythropoiesis; in a study of patients undergoing orchiectomy for metastatic prostate cancer, the incidence of anemia was significantly higher in those who received flutamide than in those who underwent orchiectomy alone ($P=0.024$).[40] In a study of 141 patients receiving radiotherapy and four months of CAB with goserelin and flutamide, hemoglobin fell by 3.1 ± 0.1 g dl^{-1} (range, 0.1–6.8 g dl^{-1}), and 81% of men experienced a hemoglobin fall of >2 g dl^{-1}.[41]

In a prospective study of 147 prostate cancer patients receiving CAB, hemoglobin levels declined significantly in all patients from a mean baseline of 14.9 g dl^{-1} to means of 13.9, 13.2 and 13.1 g dl^{-1} at 1, 2 and 3 months, respectively. Hemoglobin levels continued to decline during CAB to a mean nadir of 12.3 g dl^{-1} at a mean of 5.6 months of CAB, representing a mean absolute hemoglobin decline at nadir of 2.5 g dl^{-1}. In 13% of patients, the relative decline in hemoglobin was $\geqslant$25%, representing a mean absolute hemoglobin decline in this subset of 4.3 g dl^{-1}. Significant symptoms related to anemia occurred in 17 patients (13%).[42] In a cohort of patients with longer follow-up, hemoglobin declined, from a mean baseline of 14.8 g dl^{-1}, to a minimum of 10.5 g dl^{-1} ($P<0.0001$) 24 months after the initiation of androgen suppression.[43] These studies suggest that the effects of ADT on erythropoiesis may be duration-dependent and that longer treatment may promote larger decreases in hemoglobin, although this requires further study. In the post-androgen suppression period, the recovery of hemoglobin was slow and followed that of testosterone. The three QoL domains tested did not show any significant correlation with the change in hemoglobin.[43] Similarly, in a small case–control study of prostate cancer patients receiving ADT compared to healthy controls, although hemoglobin was lower 13.4 g dl^{-1} *vs.* 14.8 g dl^{-1} ($P<0.001$) in men receiving ADT, there was no correlation between hemoglobin level and fatigue.[44]

SIGNIFICANCE OF ADT-INDUCED ANEMIA

The above studies show that, in patients with non-metastatic prostate cancer without anemia at baseline, ADT predictably causes, in patients treated with gonadotropin-releasing hormone agonist therapy or with orchiectomy, a relatively small (1–2 g dl^{-1}) fall in hemoglobin. This commonly leads to mild normochromic and normocytic anemia which

Table 1 Effects of androgen deprivation therapy on hemoglobin levels in longitudinal observational studies of men with non-metastatic prostate cancer

Study	n	*Age (year)*	*Baseline Hb (g dl^{-1})*	*Type and duration of ADT*[a]	*Nadir Hb (g dl^{-1})*	*Comments*
Fonseca *et al.*[39]	64	68	14.8	Orchidectomy	13.4	78% had median decrease in Hb of at least 1 g dl^{-1}, and 29% of at least 2 g dl^{-1}. Maximal decrease in Hb occurred at median of 349 days
Asbell *et al.*[41]	141	79	N.R.	CAB for 4 months	-3.1[b]	Mean Hb decrease was -2.1 g dl^{-1} at 2 months, and -3.1 g dl^{-1} in 4 months
Strum *et al.*[42]	147	76	14.9	CAB for $\geqslant$6 months	12.3	Mean Hb decline from baseline was 1.0 g dl^{-1} at 1 month, and 1.8 g dl^{-1} at 3 months of therapy. Nadir Hb occurred at mean of 5.6 months
Choo *et al.*[43]	72	64	14.8	GnRH agonist for 24 months	10.5	Nadir Hb occurred at 24 months
D'Amico *et al.*[51]	110	70	14.8	CAB for 6 months	12.9	Nadir Hb occurred at 3 months, and was lower, 11.7 g dl^{-1} for the subgroup of 10 men which experienced a PSA recurrence during follow-up

Abbreviation: ADT, androgen deprivation therapy; CAB, combined androgen blockade; GnRH, gonadotrophin-releasing hormone; Hb, hemoglobin; N.R., not reported; PSA, prostate-specific antigen.

[a] Men received concurrent pelvic radiotherapy.

[b] Hb decrease from baseline.

is not usually associated with significant clinical consequences in the majority of patients. However, anemia can be more severe and become clinically significant in a minority of patients. More severe anemia is more likely to occur in patients with metastatic prostate cancer with diminished bone marrow reserve, and in those receiving CAB, because this treatment removes residual hemopoietic effects of adrenally-derived androgens. More severe anemia is also more common with prolonged duration of ADT. In patients with metastatic prostate cancer and pre-existing, cancer-associated anemia, however, the ADT-associated reduction in cancer burden may exceed the reduction in hemoglobin level caused by androgen loss. Indeed, in a study of men with metastatic prostate cancer receiving ADT, hemoglobin levels actually increased in patients who were anemic prior to therapy, but decreased in patients with no anemia at baseline.[45]

In clinical studies, the reported prevalence of symptomatic anemia varied widely, ranging from 0%[46] to 43%.[47] This variability is explained by the nonspecific nature of anemic symptoms and by study limitations, which include small size, non-randomized design, differences in study population characteristics and ADT treatment modalities, and limited adjustment for confounders. Thus, studies to date have not been designed to adequately assess the contribution of anemia to ADT-associated fatigue, decreased physical functioning, angina, cardiac failure and QoL. Clearly, fatigue in patients with prostate cancer is multifactorial and contributed to by ADT-associated sarcopenia and mood changes, which in turn are superimposed on the underlying cancer-related fatigue, and modulated by comorbidities. Symptoms caused by anemia, such as fatigue, dyspnea and tachycardia, may decrease QoL and impede daily activities. Significant anemia may aggravate weakness due to ADT-induced sarcopenia. Severe anemia may also increase falls and therefore fracture risk, and increase cardiovascular risk. This is of concern as ADT leads to micro-architectural decay of bone,[4] causes insulin resistance,[48] and may increase cardiovascular risk (for review, see Grossmann *et al.*,[1,3,5] and articles elsewhere in this issue).

PROGNOSTIC IMPACT OF ANEMIA IN PROSTATE CANCER

The overall prevalence of anemia in men with prostate cancer is 30%, and low hemoglobin levels correlate significantly with poor performance status.[49] In addition, anemia is a well-established, independent prognostic marker of poor outcome in men with prostate cancer, increasing the relative risk of death by 47% (21%–78%).[50] Interestingly, a more marked hemoglobin decline with ADT may also predict a poorer prognosis. In a cohort of men with newly diagnosed, metastatic prostate cancer, the decline in hemoglobin after 3 months of ADT was associated, after adjustment for confounders including the baseline hemoglobin, with shorter survival (hazards ratio: 1.10 per 1 g dl^{-1} decline; $P=0.0035$) and shorter progression-free survival (hazards ratio: 1.08 per 1 g dl^{-1} decline; $P=0.013$). Similarly, a decline in hemoglobin of $\geqslant$1 g dl^{-1} during the first month of neoadjuvant ADT was reported to be, in multivariate analyses, the only independent predictor of early recurrence in patients who received neoadjuvant ADT followed by radiation for high-risk, localized prostate cancer.[51] Whether this decline of hemoglobin is a marker of more aggressive disease or contributes to resistance to therapy is unknown. Anemia may either be a cause of tumor resistance by leading to tumor hypoxia, or share a common pathophysiogical factor with tumor resistance, such as cytokine-mediated inflammation.[45] However, it is not known whether correction of anemia improves prognosis.

EVALUATION OF ADT-ASSOCIATED ANEMIA

While the knowledge of the phenomenon of ADT-induced anemia can prevent an unnecessary extensive diagnostic evaluation in men with mild, normochromic and normocytic anemia, significant anemia should not be solely attributed to ADT, and should be investigated appropriately (**Figure 1**). Patients should be assessed for treatable risk factors of anemia prior to commencement of ADT (iron stores, vitamin B12 and folate), and underlying causes should be addressed in men who have anemia prior to ADT initiation. Causes of anemia in addition to ADT in men with prostate cancer include: bone marrow infiltration from metastatic prostate cancer, treatment-related myelotoxicity (radiation, chemotherapy), radiation proctitis or cystitis, anemia of chronic disease, inflammatory cytokines, hematuria, poor nutrition and an age-related increase in susceptibility to anemia.[52] In addition, hemoglobin should be measured at regular intervals in patients receiving ADT, although frequency of hemoglobin measurements need to be individualized according to symptoms and baseline hemoglobin level.

TREATMENT OF ADT-ASSOCIATED ANEMIA

While the majority of patients with mild anemia require no treatment, symptomatic patients with more severe anemia will require treatment, after exclusion of other causes. Treatment will need to be individualized, and risk/benefit ratio of treatment modalities such as erythropoiesis-stimulating agents (ESAs) will need to be considered. In patients with severe anemia, metastatic cancer and limited bone marrow reserve, regular blood transfusions may be the only effective measure. Iron and vitamin B12/folate supplementation should be given to correct any deficiencies. Malnutrition should be addressed by dietary means, and in men who are underweight or losing weight, depression should be excluded.

Although animal[53] and human[54] studies suggest that erythropoietin deficiency does not contribute to castration-induced anemia, pharmacotherapy with erythropoietin or other ESAs has been demonstrated to improve ADT-associated anemia. However, the risk/benefit ratio of ESA therapy in men with prostate cancer remains uncertain. Concerns regarding erythropoietin therapy stem from preclinical evidence showing erythropoietin receptor expression on neoplastic cells including prostate cancer cells.[55] Moreover, erythropoietin may stimulate Leydig cell testosterone production *via* a specific, erythropoietin receptor-mediated mechanism.[56] Finally, erythropoietin promotes angiogenesis and may therefore stimulate tumor growth.

In randomized clinical trials of patients with or without cancer, therapy with ESAs, while reducing transfusion requirements and improving QoL in patients with symptomatic anemia, has been associated with an increased risk of thrombovascular events, and the impact of ESAs on overall survival and mortality remains controversial despite several meta-analyses.[57] One meta-analysis of 51 clinical trials with 13 611 cancer patients found patients who received ESAs had an increased mortality risk (hazard ratio: 1.10; 95% CI: 1.01–1.20) and an increased risk of venous-thromboembolic events (VTEs) (7.5% *vs.* 4.9%; relative risk: 1.57; 95% CI: 1.31–1.87).[58] In contrast, a more recent meta-analysis of 60 studies (15 323 cancer patients) has shown that ESA use did not significantly affect mortality (60 studies: OR: 1.06; 95% CI: 0.97–1.15) or disease progression (26 studies: OR: 1.01; 95% CI: 0.90–1.14), but increased the risk for VTE (44 studies: OR: 1.48; 95% CI: 1.28–1.72).[59] The risk of VTE increased with higher ($>$12–13 g dl^{-1}) target hemoglobin levels.[57–59] While phase III randomized trials of ESAs specifically in prostate cancer patients have reported hematological responses and favorable trends in QoL, none has been designed or powered to formally address their effect on overall survival and tumor recurrence.[60] In addition, a recent study has suggested that ADT, by itself, may increase the risk of VTEs.[61] However, there is no evidence that ADT and ESAs have additive effects on VTE risk.

Clinicians wishing to prescribe ESAs to prostate cancer patients should take note of updated guidelines, provided by the National

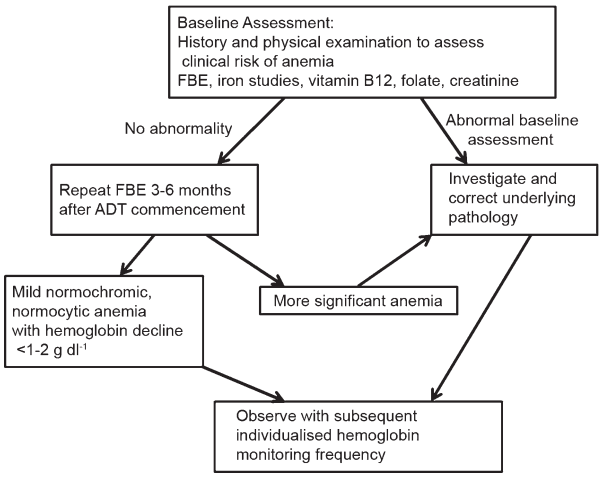

Figure 1 Suggested approach to assessment and monitoring for anemia in men receiving ADT. ADT, androgen deprivation therapy; FBE, full blood exam.

Comprehensive Cancer Network (http://www.nccn.org/professionals/physician_gls/f_guidelines.asp). Evidence for medical treatment options for anemia other than ESAs is limited. In one uncontrolled study of 37 Japanese patients with hormone-refractory prostate cancer receiving low-dose dexamethasone (0.5–2 mg d^{-1}), 65% had an increase in hemoglobin, and 33% achieved an increase of $\geqslant 2$ g dl^{-1} after 1 month of treatment.[62]

EFFECTS OF ANDROGENS ON WHITE BLOOD CELLS AND PLATELETS

The recent literature on the effects of androgens on hemopoietic cells other than the red blood cell lineage is scarce. The predominant hematological phenotype of male mice genetically engineered to lack the androgen receptor (androgen receptor knockout mice) was neutropenia with increased susceptibility to microbial infection.[63] Surprisingly, androgen receptor knockout mice did not have reduced hemoglobin levels compared to wild-type mice, although there was a significant reduction in hematocrit.[63] In contrast to the marked neutropenia observed in androgen receptor knockout mice, castration of male mice resulted in only moderate neutrophil reduction in mice indicating that it is the androgen receptor itself rather than testosterone which is critical for neutrophil development and maturation.[63] Consistent with this, neutropenia or increased susceptibility to infection is not recognized in hypogonadal men or men receiving ADT.

Androgens exert inhibitory effects on B lymphopoiesis which may be mediated through androgen receptors expressed in immature B lymphocytes and in bone marrow stromal cells.[64] This is consistent with findings that castration of normal mice leads to splenic enlargement and expansion of the B-cell population which can be reversed with androgen treatment.[65] Androgen receptors expressed by the thymic epithelium have been shown to modulate thymus size and T-lymphocyte development.[66] There is, however, little data indicating that such findings are relevant for the sex difference in susceptibility to autoimmune disease in humans, or indeed for men receiving ADT.

Androgens have also been implicated in the regulation of thrombopoiesis, consistent with the observation that the androgen receptor is expressed in megakaryocytes and regulated by androgens.[67] Thrombocytosis has been reported in abusers of anabolic steroids,[68] and increases in platelet counts have been observed in patients receiving androgen treatment for aplastic anemia.[10] Testosterone increases human platelet aggregation responses *via* increases in human platelet A2 receptor density,[68] and it has been speculated that this may contribute to the thrombogenicity of anabolic steroids. Again, significant abnormalities in platelet count in men with prostate cancer receiving ADT have not been reported.

In summary, while there is preclinical evidence and limited data from humans that androgens may regulate hemopoietic lineages other than red blood cells, effects of ADT on white blood cells and platelets have not been carefully studied. Our clinical experience suggests that effects of ADT on such cells are unlikely to be of major clinical significance.

CONCLUSIONS

Prior to commencement of ADT, all patients should be counseled about ADT-associated side effects including anemia, and adverse events should be considered in the decision-making process of commencing ADT for prostate cancer, especially for indications where a survival benefit of ADT has not been established. Given the diverse nature of ADT-associated adverse effects, management of patients with prostate cancer receiving ADT should consist of an individualized, multidisciplinary approach by clinicians with expertise and interest in this problem. To formalize this process, we have recently developed evidence-based guidelines for management of men with prostate cancer receiving ADT on behalf of the Endocrine Society of Australia, the Australian and New Zealand Bone and Mineral Society, and the Urological Society of Australia and New Zealand.[3]

Unfortunately, current information is inadequate to assess the risk-benefit ratio of ADT for a large proportion of men with prostate cancer. Therefore, controlled trials are required to assess the effect of ADT on survival in men with low-risk prostate cancer, to determine the optimal length of ADT for specific patient populations, and to investigate the role of using intermittent ADT to minimize adverse effects while maintaining anti-tumor efficacy. Such information will be crucial to better define the risk/benefit ratio for ADT for the individual patient with prostate cancer. In addition, the impact of anemia, and of its treatment on QoL and survival requires further study. Whether the effects of androgens on white blood cells and platelets described in preclinical studies are of relevance to men receiving ADT is currently unknown.

COMPETING FINANCIAL INTERESTS

All authors declare that there are no competing financial interests.

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