Editorial

Prognostic factors during androgen deprivation therapy in patients with hormone naive metastatic prostate cancer: is changes in hemoglobin level significant?

Daisaku Hirano, Toshiyuki Yoshida

Department of Urology, Higashimatsuyama Municipal Hospital, Higashimatusyama, Saitama, Japan

Correspondence to: Daisaku Hirano, MD. Department of Urology, Higashimatsuyama Municipal Hospital, 2392 Oaza Matsuyama Higashimatusyama, Saitama 355-005, Japan. Email: byd04561@nifty.com.

Comment on: Ebbinge M, Berglund A, Varenhorst E, *et al.* Clinical and prognostic significance of changes in haemoglobin concentration during 1 year of androgen-deprivation therapy for hormone-naïve bone-metastatic prostate cancer. BJU Int 2018. [Epub ahead of print].

Received: 31 July 2018; Accepted: 03 September 2018; Published: 25 September 2018.

doi: 10.21037/amj.2018.09.01

View this article at: http://dx.doi.org/10.21037/amj.2018.09.01

Androgen deprivation therapy (ADT) or combined with first-generation anti-androgen drugs such as bicalutamide and flutamide have been chosen as first line for hormone naïve metastatic prostate cancer. Recently, adding chemotherapeutic agent, docetaxel, to ADT improved patient survival, and is becoming a new standard for patients with hormone naïve metastatic high volume disease (1). In more recent studies, adding second generation androgen receptor targeting agent such as abiraterone to ADT had a similar benefit to docetaxel with less toxicities, and some experts recommend to use this agent for patients with hormone naïve metastatic high volume prostate cancer as first line (2). However, ADT is a still gold standard care for hormone naïve metastatic prostate cancer in worldwide.

The majority of patients with hormone naïve metastatic prostate cancer response initially to ADT, however, it is difficult to predict the response to the therapy and the duration of treatment for the individual patient (3). Additionally, there is potential for much longer term use of ADT as survival times will be extended and there are also the adverse effects such as the risks of sexual dysfunction, diabetes mellitus, cardiovascular diseases, osteoporosis, obesity, muscle weakness and anemia (4).

During the treatment with ADT it is important to consider prognostic variables that have been identified as markers of determining the likelihood of response. Pretreatment prognostic factors such as Gleason score, T category, prostate-specific antigen (PSA), alkaline phosphatase, hemoglobin, performance status, extensive disease including cancer-related pain and comorbidities, are useful for identifying which patients are less likely to respond to the treatment, and this information also could support to counsel patients as well. In term of prognostic markers during ADT, the most attractive study, Southwest Oncology Group (SWOG) trial, showed in PSA kinetics after initiation of ADT for new M1 prostate cancer initial PSA nadir 7 months after initiation of luteinizing hormone-releasing hormone (LH-RH) agonist was a strong predictor of median overall survival (5). They identified that patients who had a PSA nadir of ≤0.2 ng/mL at 7 months after the initiation of therapy had a median overall survival of 75 months, in contrast patients who experienced a PSA nadir of >4 ng/mL had a median overall survival of only 13 months, and patients who had a PSA nadir of 0.2–4.0 ng/mL had median overall survival of 44 months. They concluded that PSA nadir at 7 months response to initial ADT for M1 hormone naïve prostate cancer is important for prognosis during ADT. The PSA kinetics is a powerful prognostic factor.

In the setting of the treatment of hormone naïve metastatic prostate cancer achieving a low testosterone level is also greatly important. The traditional testosterone level to define a castrate status has been 50 ng/dL or less (6). However, Morote *et al.* (7) identified patients who failed to achieve testosterone levels below 20 ng/dL had a more rapid progression toward castrate-resistant disease. Additionally, Perachino *et al.* (8) also reported that testosterone level measured after 8 months of initial hormone therapy was

a strong predictor of progression to castrate-resistant disease. They suggested that young patients with age of less than 70-year-old predicted higher risk for testosterone breakthrough of testosterone above 50 ng/dL in during ADT. The kinetics of testosterone levels during ATD is a prognostic factor as well.

As to the other prognostic makers during ADT SWOG S8894 study revealed the relationship between the kinetics of hemoglobin levels and ADT (9). The clinical trial included available 817 patients with metastatic prostatic carcinoma for analysis of change in hemoglobin levels after 3 months initiation of ADT with or without flutamide, and resulted in the mean hemoglobin level declined 0.54 g/dL at 3 months after initiating ADT, and after adjusting for potential confounders, a decrease in hemoglobin levels after 3-month of ADT was independently related to shorter survival and shorter progression-free survival.

The present study by Ebbinge *et al.* (10) was conducted to evaluate changes in hemoglobin levels during the first 12 months of ADT as a predictor of prognosis in patients with hormone naïve prostate cancer who had bone-metastatic (stage M1b) based on the Scandinavian Prostate Cancer Group (SPCG) trial no. 5, a phase III study. The study consisted of 302 patients treated with total androgen blockade (bilateral orchiectomy or medical castration with LH-RH agonist combined with 250 mg flutamide orally three times daily) and 295 patients received polyestradiol phosphate (240 mg) with intramuscular injection every 2 weeks for 8 weeks and monthly thereafter. They measured hemoglobin at enrolment, 3, 6 and 12 months of ADT, and analyzed the time-dependent impact of changes in hemoglobin levels on overall survival. Multivariate analysis of changes in hemoglobin level between baseline and 3 months revealed a favorable survival in patients with a decline in hemoglobin level with hazard ratio of 1.42 compared to those with an increase. In contrast unfavorable survival was identified in patients with a decrease in hemoglobin levels between 6 and 12 months with hazard ration of 0.76 compared to those with an increase. They concluded that assessment of changes in hemoglobin levels during 12 months of ADT for hormone naïve bone metastatic prostate cancer is useful for prospect of prognosis, and proposed to conduct its use as a monitoring. Although their study confirmed the impact of changes in hemoglobin levels on the prognosis of advanced prostate cancer patients receiving ADT, the outcomes in changes of hemoglobin levels between baseline and 3 months were opposite to those of the SWOG 8894 study (9). The data mismatch both the studies might be caused by different hormone therapies and population. In the present study by Ebbinge *et al.* (10) approximately 50% of the patients were treated with polyestradiol phosphate. Some investigators reported that haematopoietic stem cells were shown to respond to estrogen (11). Although the present study by Ebbinge *et al.* (10) did not include data of sub-analysis of the relationship between changes in hemoglobin levels and type of hormone therapies for overall survival, it is speculated that the increase of changes in hemoglobin levels might be found in the most patients treated with polyestradiol phosphate, and this hormonal agent might be less effective and durable compared to the total androgen blockade. However, in the SWOG 8894 study (9) the hemoglobin levels in some patients with anemia at enrolment increased at the first 3 months after ADT, while the hemoglobin levels in the patients with no anemia at baseline decreased after ADT. For patients with cancer-associated anemia ADT may indirectly improve anemia following the therapeutic effect to cancer, but these patients are ultimately poor prognosis because of high volume disease. Thus, an increase in hemoglobin concentration at the first 3 months after ADT is likely to be an unfavorable prognostic marker.

Androgens provoke hematopoietic system by various mechanisms including stimulation of erythropoietin release, increasing bone marrow activity and iron incorporation into the red cells (12). Anemia is a common side effect of patients receiving ADT, and there is a possibility that anemia caused by ADT contributes to fatigue and affects quality of life (13). *Table 1* shows effects of ADT on hemoglobin levels in longitudinal observational studies (9,10,14-18). Combined androgen blockade has been shown to cause a more substantial reduction in erythropoiesis, Eisenberger *et al.* (19) reported that the incidence of anemia in metastatic prostate cancer patients who received combined androgen blockade with flutamide was significantly higher compared to that in those who underwent orchiectomy alone. ADT causes a relatively small fall (1–2 g/dL) in hemoglobin levels in treatment with LH-RH agonist or orchiectomy in non-metastatic prostate cancer patients without anemia at baseline (13). This mild anemia dose not usually affected significant clinical prognosis in most patients with non-metastatic or low volume disease. In contrast, anemia in patients who have metastatic high volume disease is more serious, and affects clinically significant prognosis. More serious anemia is more likely to occur in patients with advanced metastatic prostate cancer with diminished bone

Table 1 Effects of ADT on hemoglobin kinetics in patients with hormone naïve prostate cancer

Study	n	Mean age	State of disease	Baseline Hb (g/dL)	Type of ADT	Mean naidr Hb (g/dL)	Comments
Fonseca *et al.* (14)	61	68	Non-metastasis	14.8	Orchiectomy	13.4	78% had a median decline in Hb of at least 1 g/dL and 29% of at least 2 g/dL. Maximal declines in Hb occurred at median of 349 days
Asbell *et al.* (15)	141	79	Non-metastasis	NR	CAB for 4 months	NR	Mean Hb decrease ranged –2.1 g/dL at 2 months and –3.1 g/dL in 4 months
Strum *et al.* (16)	147	76	Non-metastasis	14.9	CAB ≥6 months	12.3	Mean Hb decline from baseline revealed 1.0 g/dL at 1 month, and 1.8 g/dL at 3 months of treatment. Nadir Hb was at mean of 5.6 months
Choo *et al.* (17)	72	64	Non-metastasis	14.8	GnRH agonist for 24 months	10.5	Nadir Hb was at 24 months
D'Amico *et al.* (18)	110	70	Non-metastasis	14.8	CAB for 6 months	12.9	Nadir Hb was at 3 months
Beer *et al.* (9)	817	70	Metastasis	13.3	ADT or CAB	12.7 at 3 months	Mean change of 0.54 g/dL in Hb between baseline and 3 months
Ebbinge *et al.* (10)	597	72	Metastasis	NR	CAB or polyestradiol phosphate	NR	Coefficient of –0.52 in charge of Hb from baseline to 3 months

ADT, androgen deprivation therapy; CAB, combined androgen blockade; NR, not report.

marrow reserve, and in those receiving ADT result in more severe anemia and also more common with prolonged duration of ADT. In these high volume disease patients hemoglobin levels at base line are low, and likely to develop to easy decline after ADT and get castration-resistant prostate cancer. Thus, evaluating hemoglobin kinetics during ADT is definitively useful for monitoring such patients who have hormone naïve high volume metastatic prostate cancer and prospecting their prognosis.

Acknowledgements

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned and reviewed by the Section Editor Xiao Li (Department of Urologic Surgery, the Affiliated Cancer Hospital of Jiangsu Province of Nanjing Medical University, Nanjing, China).

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/amj.2018.09.01). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. N Engl J Med 2015;373:737-46.
2. Elkon JM, Millett RL, Millado KF, et al. Abiraterone is effective and should be considered for the treatment of

metastatic castrate-naïve prostate cancer. Expert Opin Pharmacother 2018;19:507-9.
3. Loblaw DA, Virgo KS, Nam R, et al. Initial hormonal management of androgen-sensitive metastatic, recurrent, or progressive prostate cancer: 2006 update of an American Society of Clinical Oncology practice guideline. J Clin Oncol 2007;25:1596-605.
4. Higano CS. Side effects of androgen deprivation therapy: monitoring and minimizing toxicity. Urology 2003;61:32-8.
5. Hussain M, Tangen CM, Higano C, et al. Absolute prostate-specific actigen value after androgen deprivation is a strong independent predictor of survival in new metastatic prostate cancer: data from Southwest Oncology Group Trial 9346 (INT-0162). J Clin Oncol 2006;24:3984-90.
6. Moul JW, Dreicer R. Focusing on testosterone. Urology 2011;78:S476-7.
7. Morote J, Orsola A, Planas J, et al. Redefining clinically significant castration levels in patients with prostate cancer receiving continuous androgen deprivation therapy. J Urol 2007;178:1290-5.
8. Perachino M, Cavalli V, Bravi F. Testosterone levels in patients with metastatic prostate cancer treated with luteinizing hormone-releasing hormone therapy: prognostic significance? BJU Int 2010;105:648-51.
9. Beer TM, Tangen CM, Bland LB, et al. The prognostic value of hemoglobin change after initiating androgen-deprivation therapy for newly diagnosed metastatic prostate cancer: A multivariate analysis of Southwest Oncology Group Study 8894. Cancer 2006;107:489-96.
10. Ebbinge M, Berglund A, Varenhorst E, et al. Clinical and prognostic significance of changes in haemoglobin concentration during 1 year of androgen-deprivation therapy for hormone-naïve bone-metastatic prostate cancer. BJU Int 2018. [Epub ahead of print].
11. Nakada D, Oguro H, Levi BP, et al. Oestrogen increases haematopoietic stem-cell self-renewal in females and during pregnancy. Nature 2014;505:555-8.
12. Shahani S, Braqa-Basaria M, Maggio M, et al. Androgens and erythropoiesis: past and present. J Endocrinol Invest 2009;32:704-16.
13. Grossmann M, Zajac JD. Hematological changes during androgen deprivation therapy. Asian J Androl 2012;14:187-92.
14. Fonseca R, Rajkumar SV, White WL, et al. Anemia after orchiectomy. Am J Hematol 1998;59:230-3.
15. Asbell SO, Leon SA, Tester WJ, et al. Development of anemia and recovery in prostate cancer patients treated with combined androgen blockade and radiotherapy. Prostate 1996;29:243-8.
16. Strum SB, McDermed JE, Scholz MC, et al. Anemia associated with androgen deprivation in patients with prostate cancer receiving combined hormone blockade. Br J Urol 1997;79:933-41.
17. Choo R, Chander S, Danjoux C, et al. How are hemoglobin levels affected by androgen deprivation in non-metastatic prostate cancer patients? Can J Urol 2005;12:2547-52.
18. D'Amico AV, Saegaert T, Chen MH, et al. Initial decline in hemoglobin during neoadjuvant hormone therapy predicts for early prostate specific antigen failure following radiation and hormonal therapy for patients with intermediate and high-risk prostate cancer. Cancer 2002;95:275-80.
19. Eisenberger MA, Blumenstein BA, Crawford ED, et al. Bilateral orchiectomy with or without flutamide for metastatic prostate cancer. N Engl J Med 1998;339:1036-42.

doi: 10.21037/amj.2018.09.01
Cite this article as: Hirano D, Yoshida T. Prognostic factors during androgen deprivation therapy in patients with hormone naive metastatic prostate cancer: is changes in hemoglobin level significant? AME Med J 2018;3:92.

