Anaemia and iron deficiency in advanced prostate cancer: revisiting a common morbidity

Chris HM Wong, MRCS, MB, ChB, **Ivan CH Ko,** MRCS, MB, ChB, **David KW Leung,** FRCSEd, **HC Chan,** FRCSEd, FHKAM (Surgery), **KM Li,** FRCSEd, FHKAM (Surgery), **YS Chan,** FRCSEd, FHKAM (Surgery), **Francis CH Wong,** FRCSEd, FHKAM (Surgery), **Peter KF Chiu,** FRCSEd, FHKAM (Surgery), **Jeremy YC Teoh,** FRCSEd, FHKAM (Surgery), **CF Ng *,** FRCSEd, FHKAM (Surgery)

SH Ho Urology Centre, Department of Surgery, The Chinese University of Hong Kong, Hong Kong SAR, China

* Corresponding author: ngcf@surgery.cuhk.edu.hk

This article was published on 8 Apr 2025 at www.hkmj.org.

Hong Kong Med J 2025;31:154–8
https://doi.org/10.12809/hkmj2411653

Introduction

Anaemia is a common morbidity associated with malignancies at various stages. The reported prevalence of anaemia ranges from 20% to 60% in solid organ tumours.[1] The pathophysiology of cancer-related anaemia (CRA) is multifactorial. Contributing mechanisms include chronic inflammatory reactions; activation of proinflammatory cytokines such as interleukin-6, interleukin-1, and tumour necrosis factor alpha; nutritional deficiencies; bone marrow infiltration; and haemolysis. The relative contributions of these factors vary across malignancies that affect different organ systems.[2] Cancer-related anaemia can result in substantial morbidity and impaired quality of life. Its symptoms are broad, encompassing fatigue, depression, cognitive impairment, syncope, and falls.[3] Symptoms may emerge when haemoglobin levels fall below 11.5 g/dL, a threshold classified as mild anaemia by most physicians.[4] In oncological contexts, there is evidence of negative relationships between anaemia and overall outcomes. A meta-analysis of solid and haematological malignancies revealed a 65% increase in overall mortality among patients with anaemia relative to those without.[5]

Anaemia in prostate cancer: causes and incidence

Anaemia has been widely associated with advanced prostate cancer (CaP), particularly in metastatic stages treated with androgen deprivation therapy (ADT). Haematuria resulting from tumour invasion into the urethra is one potential cause.[6] Marrow suppression due to diffuse bone metastases, as well as CaP therapies (eg, radiotherapy, chemotherapy, and long-term ADT) may also contribute to reduced erythropoietin production and, consequently, lower haemoglobin levels.

The incidence of anaemia in CaP remains largely uncertain, despite its common association with clinical management. Based on inferences from published studies, the prevalence of anaemia in CaP patients ranges from 13% to 78%.[7-9] These figures substantially vary due to differences in inclusion criteria and distinct definitions of prostate CRA. Efforts to identify the true incidence of anaemia in CaP are challenging because it arises from multiple causes and produces symptoms analogous to those of advanced malignancy. Limitations concerning population- or registry-based databases further complicate assessment, given that exact blood parameters are often omitted. We share our findings regarding the incidence of anaemia in a local cohort of CaP patients and identify potential associated factors. We aim to enhance recognition of this common co-morbidity and facilitate timely management.

Prostate cancer-associated anaemia: why does it matter?

The impact of anaemia in CaP appears to extend beyond quality-of-life-related symptoms. A meta-analysis of 15 retrospective and prospective studies concluded that anaemia was associated with worse overall survival and progression-free survival.[7] There is speculation that anaemia-induced hypoxia within cancer colonies reduces reactive oxygen species levels. The downstream effect is dimerisation of hypoxia-inducible factor 1 alpha and beta, leading to the transcription of treatment resistance-associated oncogenes[8] and, ultimately, the development of castration-resistant prostate cancer (CRPC). These findings highlight the importance of early identification and prompt treatment of prostate CRA in the outpatient setting to preserve long-term oncological outcomes in advanced CaP treatment.

Implications of androgen deprivation therapy

In the management of high-risk localised, locally advanced, and metastatic prostate cancer, ADT plays a crucial role; treatment durations range from 2 years to lifelong. Its influence on the development of anaemia in this patient population cannot be understated. In a randomised controlled study involving 141 patients scheduled for radiotherapy,

Asbell et al[9] investigated changes in haemoglobin levels after radiotherapy and ADT with maximal androgen blockade among patients with localised and advanced CaP. A decrease in haemoglobin level of up to 2 g/L was reported after the initiation of maximal androgen blockade; differences emerged as early as 2 months post-initiation. A Taiwanese population-based registry study by Wu et al,[10] examining the relationship between iron deficiency and prostate cancer treatment in 10 893 cases with and without ADT (segregated according to registry coding), revealed a hazard ratio of 1.60, indicating increased likelihood of iron deficiency among patients receiving ADT. Similar effects have been detected in Western populations. Timilshina et al[11] identified ADT use as an independent predictor of haemoglobin decline over 1 year, whereas Choo et al[12] reported a decline in haemoglobin levels over 2 years in a cohort of 72 patients receiving adjuvant ADT plus radiotherapy.

The relationship between testosterone and haemoglobin synthesis has been suggested to arise from a synergistic effect on erythropoietin. Through its downstream effects, testosterone enhances the action of polychromatophilic erythroblasts and supports the activities of polymerases I and II in conjunction with erythropoietin.[7] An ADT-induced lack of testosterone may impair haematopoiesis and contribute to anaemia.

Associations of prostate cancer with anaemia and iron deficiency: findings from a local cohort

Consecutive patients were recruited from the prostate cancer clinic within a general urology unit. Ethics approval was approved by the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (Ref No.: 2014.251) and registered in ClinicalTrials.gov (Identifier: NCT03344835). Patients with a history of gastrointestinal or haematological cancer were excluded because these conditions represent significant confounders in the development of anaemia. Individuals exhibiting active symptoms of gastrointestinal bleeding or a positive faecal occult blood test result pending further evaluation were also excluded. Additionally, patients with a prior diagnosis of iron deficiency and ongoing iron supplementation were excluded.

The definition of anaemia in this study adhered to World Health Organization criteria; a haemoglobin level of 13 g/dL served as the threshold.[13] Iron deficiency was defined as a ferritin level <100 μg/L or transferrin saturation <20%. Iron deficiency anaemia was classified as the coexistence of both anaemia and iron deficiency.[14] Anaemia of chronic disease was characterised by a low serum iron level without evidence of depleted iron stores.[15] A state of CRPC was defined by a testosterone level <1.7 nmol/dL, in accordance with European Association of Urology guidelines.[16]

For sample size calculation, we regarded the proportion of anaemia within the cohort as a proportional variable. Assuming d=0.08, α=0.2, and p=0.5, the calculated sample size required for the survey was 65. Statistical analysis was performed using SPSS software (Windows version 24.0; IBM Corp, Armonk [NY], United States). Missing data were handled using mean substitution. Because no significant missing data were anticipated, sensitivity analysis was not planned. Categorical variables were represented as percentages, whereas continuous variables were expressed as mean values. Multivariate regression analysis was planned to identify confounding factors influencing outcomes. A two-tailed P value <0.05 was considered statistically significant.

Overall, 82 eligible patients recruited from September to December 2022 were included in the analysis (Table 1). The mean age of the cohort

TABLE 1. Background characteristics of the study population (n=82)*

	No. (%)
Clinical demographics	
Metastatic hormone-sensitive disease	21 (25.6%)
Castration-resistant status	11 (13.4%)
ISUP grade group	
1	19 (23.2%)
2	22 (26.8%)
3	11 (13.4%)
4	18 (22.0%)
5	8 (9.8%)
Not available	4 (4.8%)
Testosterone below castration level	44 (53.7%)
Treatment history	
Radical prostatectomy	30 (36.6%)
Radiotherapy	29 (35.4%)
Androgen deprivation therapy	50 (61.0%)
Chemotherapy	3 (3.7%)
Novel hormonal therapy	7 (8.5%)
Laboratory parameters	
Haemoglobin level, g/dL	11.9 (9.9-13.9)
Reticulocytes	1.4±1.0
Testosterone level, nmol/L	7±0.9
Creatinine, μmol/L	106.6±79.0
Albumin, g/L	40.7±7.0

Abbreviation: ISUP = International Society of Urological Pathology
* Data are shown as No. (%), median (interquartile range), or mean±standard deviation

was 74.2 years. Most patients had a performance status of 1 (67.1%). Concomitant diabetes mellitus, ischaemic heart disease, and chronic kidney disease were present in 26.8%, 7.3%, and 31.7% of patients, respectively. At the time of analysis, 25.6% of patients had metastatic hormone-sensitive CaP; 13.4% of patients had CRPC. The mean prostate-specific antigen value at diagnosis was 98.0 ng/mL, and International Society of Urological Pathology grade group 2 was most common (26.8%). More than half of the patients had castrated testosterone levels (mean testosterone level=7.0 nmol/L).

A substantial proportion of patients had anaemia (43/82, 52.4%). In total, 20.7% of patients had iron deficiency without anaemia. Among individuals with anaemia, 14.0% had iron deficiency anaemia, 7.0% had B12 deficiency, and 16.3% had folate deficiency. Anaemia of chronic disease was present in 39.5% of patients. Patients exhibiting iron deficiency anaemia were scheduled to undergo a faecal occult blood test if they had not recently completed upper and lower gastrointestinal investigations. None of the patients displayed faecal occult blood positivity. Further analysis was conducted to identify risk factors predictive of anaemia in this cohort. Univariate analysis identified a castrated state (odds ratio [OR]=1.99; P=0.002), metastatic disease (OR=1.78; P=0.004), and hypoalbuminaemia (OR=2.05; P=0.015) as statistically significant predictors of anaemia (online supplementary Table 1). Considering the observed association between a castrated state and anaemia, we performed an additional analysis to examine the relationship between haemoglobin and testosterone levels. No association was identified in analysis of the entire cohort. However, when cases were stratified by disease stage (localised, metastatic hormone-sensitive, and castration-resistant), a significant association was observed within the localised disease subgroup (effect coefficient=0.323; P=0.024) [online supplementary Table 2]; lower testosterone levels tended to be present in anaemic patients.

Multivariate analysis found that patients in a castrated state (ie, those receiving ADT) had a higher likelihood of iron deficiency (OR=1.30; P=0.006). More than half of the CRPC patients exhibited iron deficiency (OR=2.55; P=0.017). Chronic kidney disease and metastatic status were not significantly associated with iron deficiency, although slight trends were observed. Other factors, including patient age, prostate-specific antigen level at diagnosis or follow-up, performance status, and International Society of Urological Pathology grade group, were not associated with iron deficiency (Table 2).

Future directions

This study provided a snapshot of the prevalences of anaemia and iron deficiency in CaP. The incidence of anaemia was 52.4%, whereas iron deficiency was present in 20.7% of the cohort. Castration-resistant prostate cancer was associated with iron deficiency. An association between metastatic or castrated status and anaemia was also observed, reinforcing the notion that anaemia and iron deficiency are common in advanced CaP. A high level of vigilance is required among physicians responsible for the care of patients with advanced CaP, particularly during management of CRA. As highlighted in several

TABLE 2. Multivariate analysis of factors contributing to iron deficiency in a cohort of prostate cancer patients

	Not castrated	**Castrated**	**P value**
Likelihood of iron deficiency	0.226	0.294	0.006
Odds ratio	1.30		
	Non-metastatic	**Metastatic disease**	**P value**
Likelihood of iron deficiency	0.22	0.333	0.446
Odds ratio	1.52		
	Non–castration-resistant prostate cancer	**Castration-resistant prostate cancer**	**P value**
Likelihood of iron deficiency	0.224	0.571	0.017
Odds ratio	2.55		
	Normal albumin	**Hypoalbuminaemia**	**P value**
Likelihood of iron deficiency	0.25	0.5	0.34
Odds ratio	2.03		
	No chronic kidney disease	**Chronic kidney disease**	**P value**
Likelihood of iron deficiency	0.186	0.409	0.150
Odds ratio	2.20		

multicentre reviews of Asian CaP cohorts,[17-19] the consequences of anaemia may include profound adverse effects, such as metabolic complications or diminished glycaemic control. Increased awareness of CaP-related anaemia—a readily treatable condition—could improve quality of life and long-term patient outcomes.

Since the introduction of multiple antitumour treatments during earlier phases of CaP management, the treatment landscape has drastically changed in recent decades. Published studies concerning the association between prostate cancer and anaemia are largely outdated.[10,20] Future research could explore the impact of novel treatments—including androgen receptor signalling inhibitors, poly (ADP-ribose) polymerase 1 inhibitors, and prostate- or metastasis-directed radiotherapy—on CaP-related anaemia. Further studies might also assess the effectiveness of iron replacement therapy. Intravenous iron or erythropoietin[21] plays a role in the management of malignancy-related anaemia by improving patient-reported quality of life. Finally, future studies could investigate potential effects of anaemia treatment on quality-of-life measures and oncological outcomes in patients with advanced CaP.

Conclusion

Anaemia and iron deficiency are commonly observed in Asian Chinese patients with prostate cancer. Castrated and CRPC states were identified as predictors of iron deficiency in this patient population. Physicians are encouraged to monitor the development of anaemia after initiation of prostate cancer treatment. Large-scale studies may be warranted to evaluate the benefits of anti-anaemia treatment.

Author contributions

Concept or design: CF Ng, CHM Wong.
Acquisition of data: All authors.
Analysis or interpretation of data: CHM Wong.
Drafting of the manuscript: CHM Wong.
Critical revision of the manuscript for important intellectual content: All authors.

All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

As editors of the journal, JYC Teoh and CF Ng were not involved in the peer review process. Other authors have disclosed no conflicts of interest.

Funding/support

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Supplementary material

The supplementary material was provided by the authors, and some information may not have been peer reviewed. Accepted supplementary material will be published as submitted by the authors, without any editing or formatting. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by the Hong Kong Academy of Medicine and the Hong Kong Medical Association. The Hong Kong Academy of Medicine and the Hong Kong Medical Association disclaim all liability and responsibility arising from any reliance placed on the content. To view the file, please visit the journal online (https://doi.org/10.12809/hkmj2411653).

References

1. Xu H, Xu L, Page JH, et al. Incidence of anemia in patients diagnosed with solid tumors receiving chemotherapy, 2010-2013. Clin Epidemiol 2016;8:61-71.
2. Busti F, Marchi G, Ugolini S, Castagna A, Girelli D. Anemia and iron deficiency in cancer patients: role of iron replacement therapy. Pharmaceuticals (Basel) 2018;11:94.
3. van Eeden R, Rapoport BL. Current trends in the management of anaemia in solid tumours and haematological malignancies. Curr Opin Support Palliat Care 2016;10:189-94.
4. Crawford J, Cella D, Cleeland CS, et al. Relationship between changes in hemoglobin level and quality of life during chemotherapy in anemic cancer patients receiving epoetin alfa therapy. Cancer 2002;95:888-95.
5. Caro JJ, Salas M, Ward A, Goss G. Anemia as an independent prognostic factor for survival in patients with cancer: a systemic, quantitative review. Cancer 2001;91:2214-21.
6. Nalesnik JG, Mysliwiec AG, Canby-Hagino E. Anemia in men with advanced prostate cancer: incidence, etiology, and treatment. Rev Urol 2004;6:1-4.
7. Dai D, Han S, Li L, et al. Anemia is associated with poor outcomes of metastatic castration-resistant prostate cancer, a systematic review and meta-analysis. Am J Transl Res 2018;10:3877-86.
8. Varlotto J, Stevenson MA. Anemia, tumor hypoxemia, and the cancer patient. Int J Radiat Oncol Biol Phys 2005;63:25-36.
9. Asbell SO, Leon SA, Tester WJ, Brereton HD, Ago CT, Rotman M. Development of anemia and recovery in prostate cancer patients treated with combined androgen blockade and radiotherapy. Prostate 1996;29:243-8.
10. Wu FJ, Li IH, Chien WC, et al. Androgen deprivation therapy and the risk of iron-deficiency anaemia among patients with prostate cancer: a population-based cohort study. BMJ Open 2020;10:e034202.
11. Timilshina N, Hussain S, Breunis H, Alibhai SM. Predictors of hemoglobin decline in non-metastatic prostate cancer patients on androgen deprivation therapy: a matched cohort study. Support Care Cancer 2011;19:1815-21.
12. 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.
13. DeMaeyer E, Adiels-Tegman M. The prevalence of anaemia in the world [in English, French]. World Health Stat Q 1985;38:302-16.
14. Cappellini MD, Musallam KM, Taher AT. Iron deficiency anaemia revisited. J Intern Med 2020;287:153-70.

15. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. Blood 2004;104:2263-8.
16. Heidenreich A, Bastian PJ, Bellmunt J, et al. EAU guidelines on prostate cancer. Part II: Treatment of advanced, relapsing, and castration-resistant prostate cancer. Eur Urol 2014;65:467-79.
17. Wong C, Chu P, Teoh J, et al. Risks of metabolic diseases and androgen deprivation therapy for prostate cancer in a Chinese population: a prospective multi-centre cohort study. Int Urol Nephrol 2022;54:993-1000.
18. Wong CH, Xu N, Lim J, et al. Adverse metabolic consequences of androgen deprivation therapy (ADT) on Asian patients with prostate cancer: primary results from the real-life experience of ADT in Asia (READT) study. Prostate 2023;83:801-8.
19. Ng CF, Chiu PK, Yee CH, Lau BS, Leung SC, Teoh JY. Effect of androgen deprivation therapy on cardiovascular function in Chinese patients with advanced prostate cancer: a prospective cohort study. Sci Rep 2020;10:18060.
20. Fonseca R, Rajkumar SV, White WL, Tefferi A, Hoagland HC. Anemia after orchiectomy. Am J Hematol 1998;59:230-3.
21. Zhao F, Wang Y, Liu L, Bian M. Erythropoietin for cancer-associated malignant anemia: a meta-analysis. Mol Clin Oncol 2017;6:925-30.