Impact of Pretreatment Anemia on Upfront Abiraterone Acetate Therapy for Metastatic Hormone-Sensitive Prostate Cancer: A Multicenter Retrospective Study

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Abstract

Purpose: Anemia has been a known prognostic factor in metastatic hormone-sensitive prostate cancer (mHSPC). We therefore examined the effect of anemia on the efficacy of upfront abiraterone acetate (ABI) in patients with mHSPC.

Methods: We retrospectively evaluated 67 mHSPC patients with high tumor burden who received upfront ABI between 2018 and 2020 (upfront ABI group). We divided these patients into two groups: the anemia-ABI group (hemoglobin <13.0g/dL, n =21) and the non-anemia-ABI group (n =46). The primary objective was to examine the impact of anemia on the progression-free survival (PFS; clinical progression including death from any cause) of patients in the upfront ABI group. Secondary objectives included an evaluation of the prognostic significance of upfront ABI and a comparison with a historical cohort (135 mHSPC patients with high tumor burden who received androgen deprivation therapy (ADT/complete androgen blockade [CAB] group) between 2014 and 2019).

Results: We found that the anemia-ABI group had a significantly shorter PFS than the non-anemia-ABI group. A multivariate Cox regression analysis showed that anemia was an independent prognostic factor of PFS in the upfront ABI group (hazard ratio, 5.08; *P* =0.007). Patients in the non-anemia-ABI group were determined to have a significantly longer PFS than those in the non-anemia-ADT/CAB group (n =69) (*P* =0.002). However, no significant difference was observed in the PFS between patients in the anemia-ABI and the anemia-ADT/CAB groups (n =66). Multivariate analyses showed that upfront ABI could significantly prolong the PFS of patients without anemia (HR, 0.17; *P* = 0.003), whereas ABI did not prolong the PFS of patients with anemia.

Conclusion: Pretreatment anemia was a prognostic factor among mHSPC patients who received upfront ABI. Although the upfront ABI significantly improved the PFS of mHSPC patients without anemia, its efficacy in patients with anemia might be limited.

Introduction

Prostate cancer (PC) is one of the most prevalent cancers in men worldwide. [1,2] In Japan, approximately 10% of patients with PC initially present with distant metastases. [3] Most of these patients experience eventually progression to metastatic castration-resistant PC (CRPC) despite good initial response to androgen deprivation therapy (ADT). [4,5] Recently, the LATITUDE trial demonstrated that upfront abiraterone acetate (ABI, a type of androgen receptor-targeted agent [ARTA]) added to ADT can lead to significant benefits in mHSPC patients compared with ADT monotherapy. [6,7] However, these studies showed an almost similar PFS and overall survival between the ADT monotherapy and upfront ABI groups in the early term of the study. [6,7] Thus, we speculated that some important prognostic and/or predictive factors may be present among patients who received ABI therapy.

Anemia is a powerful prognostic factor in PC. [5,8] Our previous study demonstrated that pretreatment anemia was an independent prognostic factor that predicted oncological outcomes among mHSPC patients treated with ADT monotherapy or complete androgen blockade (CAB). [5] However, the prognostic significance of anemia among mHSPC patients treated with ARTA remains unclear. Therefore, we retrospectively examined the prognostic significance of pretreatment anemia on the oncological outcomes of mHSPC patients treated with upfront ABI.

Materials And Methods

This retrospective study was performed according to the ethical standards of the Declaration of Helsinki and was further approved by the ethics review board of the Hirosaki University School of Medicine (authorization number: 2019–094).

Study population and patient selection

In total, 168 mHSPC patients with high tumor burden, who were initially treated with ADT alone or CAB (ADT/CAB, n = 101) or upfront ABI therapy (n = 67), were retrospectively examined at the Hirosaki University Hospital and associated hospitals between 2008 and 2020 (Aomori database). Furthermore, we retrospectively evaluated 563 mHSPC patients with CHAARTED high-volume disease, who were in the Michinoku Japan Urological Cancer Study Group database and who were initially treated with ADT/CAB between 2008 and 2016 (Michinoku database). [4,5,9] Considering that patients with metastatic CRPC had a chance to receive ARTAs and improved their prognosis, the era of diagnosis or treatment might be associated with prognoses among mHSPC patients. We therefore excluded 22 patients treated with ADT/CAB who were diagnosed before 2014 in the Aomori database and 131 in the Michinoku database. In addition, we excluded 22 patients treated with ADT/CAB in the Aomori database and 355 in the Michinoku database due to insufficient baseline laboratory data, such as information on hemoglobin (Hb), lactate dehydrogenase (LDH), and alkaline phosphatase (ALP) (Fig. S1). Finally, 202 mHSPC patients who had high tumor burden were evaluated (Fig. 1); they were then divided into two groups: the ADT/CAB group (n = 135) and the upfront ABI group (n = 67). We further categorized the patients into the following groups based on whether they had pretreatment anemia: non-anemia-ABI (n = 46), anemia-ABI (n = 21), non-anemia-ADT/CAB (n = 69), and anemia-ADT/CAB groups (n = 66).

Variable evaluations

The following variables were examined at diagnosis: age, Eastern Cooperative Oncology Group Performance Status (ECOG-PS), Gleason score, and initial prostate-specific antigen (PSA), Hb, LDH, and ALP levels. ECOG-PS was defined as worse if ECOG-PS was of ≥ 1. [10] The cutoff value of PSA level was set at 100 ng/mL.[11] Anemia was defined as an Hb level < 13.0 g/dL. [12] The cutoff values for LDH and ALP levels were set at 222 and 322 IU/L, respectively, based on the standard common reference for clinical laboratory tests in Japan. [13] We evaluated metastatic status before treatment using chest and body computed tomography and bone scintigraphy scans. Bone metastatic volume was assessed

according to the extent of disease (EOD) score. EOD was defined as worse if EOD was of ≥ 3. [11] CRPC-free survival was evaluated from the date of the initial diagnosis of mHSPC to the date of CRPC diagnosis according to the recommendations of the Cancer Clinical Trials Working Group 2.[14]

Treatment protocol

Patients were initially treated with ADT alone or ADT plus bicalutamide before upfront ABI therapy was approved. Starting in March 2018, patients who met the LATITUDE study criteria could receive upfront ABI therapy.

Primary objective

Our primary purpose was to evaluate clinical progression (i.e., development of CRPC or death from all causes before the development of CRPC) because we had a limited number of clinical events due to a short follow-up period in the upfront ABI group. We compared the clinical PFS between patients in the anemia-ABI and those in the non-anemia-ABI groups (Analysis-1). The adverse event (AE)-related discontinuation of ABI was compared between patients with and without anemia. We then assessed the impact of anemia and other clinical factors on the PFS of patients in the upfront ABI group using Cox proportional hazard analyses. We adopted the propensity score-based inverse probability of treatment weighting (IPTW) method in order to adjust for group imbalances.

Secondary objectives

The secondary objectives of this study were to compare the PFS between patients in the non-anemia-ABI group and those in the non-anemia-ADT/CAB group (Analysis-2), and between patients in the anemia-ABI group and those in the anemia-ADT/CAB group (Analysis-3). We then assessed the efficacy of upfront ABI on the PFS using multivariate Cox proportional hazard analyses or IPTW-adjusted analyses.

Statistical analysis

Statistical analyses were conducted using GraphPad Prism 5.03 (GraphPad Software, San Diego, CA, USA), EzR (R commander version 1.6–3), and R 3.3.2 (The R Foundation for Statistical Computing, Vienna, Austria). Categorical variables were compared using Fisher's exact test or chi-squared test. Quantitative variables are then expressed as means with standard deviations or as medians with interquartile ranges (IQRs). The statistical difference between groups was compared using Student's *t*-test for normally distributed data or Mann–Whitney *U*-test for non-normally distributed data. The PFS was estimated and compared using the Kaplan–Meier curve and log-rank test, respectively. In case of limited event numbers, we adopted an IPTW-adjusted multivariable Cox regression analysis. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated after controlling for potential confounders. *P*-values < 0.05 were considered to be statistically significant.

Results

Primary objective

We found significant differences in the ECOG-PS (P = 0.019), initial PSA (P = 0.001), EOD (P = 0.006), ALP (P = 0.026), and LDH (P = 0.018) between the non-anemia-ABI and anemia-ABI group (Table 1). Three patients discontinued ABI therapy due to severe AEs (two for liver damage and one for hyponatremia). No difference was observed in the rate of AE-related discontinuation of ABI between the two groups. During the median follow-up period of 13 months, 16 patients in the upfront ABI group experienced clinical progression (Table 1). Fourteen patients developed CRPC (nine in the anemia-ABI group), and two patients in the anemia-ABI group died before the development of CRPC. Of the 14 patients who developed CRPC, 2 died from PC. We observed a significantly longer PFS in the non-anemia-ABI group compared with that of the anemia-ABI group (P < 0.001) (Fig. 2A). Univariate Cox regression analyses in the ABI group showed that an LDH level > 222 IU/L (HR, 3.04; P = 0.034) and anemia (HR, 6.04; P < 0.001) were significantly associated with worse PFS (Table 2). IPTW-adjusted multivariate Cox regression analyses revealed that anemia (HR, 5.08; P = 0.007) was independently associated with worse PFS, while an LDH level > 222 IU/L was not (Fig. 2B).

Secondary objectives

Table S1 illustrates a comparison of the characteristics between patients in the upfront ABI and ADT/CAB groups, according to the presence or absence of anemia. No significant group-difference was observed other than follow-up period between the non-anemia-ABI and non-anemia-ADT/CAB group, between the anemia-ABI and anemia-ADT/CAB group. Our additional study showed that patients in the upfront ABI group had a significantly longer PFS than those in the ADT/CAB group in the entire cohort (P < 0.001) (Fig. S2A). Similarly, the PFS in the non-anemia-ABI group was significantly superior to that in the non-anemia-ADT/CAB group (P < 0.001) (Fig. 3A). However, the PFS of patients in the anemia-ABI group did not have a significantly longer than that of patients in the anemia-ADT/CAB group (P = 0.270) (Fig. 3B). The IPTW adjusted-multivariable Cox regression analysis revealed that upfront ABI therapy was significantly associated with prolonged PFS in patients without anemia (HR, 0.17; P = 0.003) (Fig. 3C top), whereas this was not observed in patients with anemia (HR, 0.63; P = 0.206) (Fig. 3C bottom).

Discussion

We compared the PFS between mHSPC patients with anemia and those without anemia in the upfront ABI group. We found an independent association between pretreatment anemia and the efficacy of upfront ABI therapy. As the LATITUDE trial has shown [6,7], our study demonstrated the efficacy of upfront ABI therapy for mHSPC patients with high-tumor burden. This trend was remarkable especially in patients without anemia. However, we did not observe any meaningful difference in PFS between patients with anemia in the upfront ABI group and those in the ADT/CAB group. To the best of our knowledge, this is the first study demonstrating between pretreatment anemia and clinical outcome in patients treated with ARTA.

Anemia has been identified as one of the most prevalent characteristics of malignancies.[15] Among mHSPC patients, the prevalence of pretreatment anemia was as high as 44–50%. [5,16] This study showed

that the prevalence of anemia in this entire cohort was 43%. Anemia in mHSPC patients may be attributed to several factors, including malnutrition and chronic inflammation. [5,17] Our previous study demonstrated that 85% of mHSPC patients with malnutrition were diagnosed with anemia. [5] Furthermore, the Hb level was inversely correlated with interleukin-6 expression, oxidative stress markers, and C-reactive protein level among patients with advanced cancer, which implied that inflammatory status is associated with worse iron metabolism in advanced cancers. [18] The relationship among anemia, malnutrition, and inflammatory status may be largely explained by cancer cachexia. Cancer cachexia is a complex syndrome that is often characterized by severe fatigue and progressive weight loss and is caused by a cancer-induced negative protein and energy balance as well as by inflammation. Malnutrition and inflammation suppress protein synthesis, particularly in advance caners, and it may also suppress erythropoiesis.[19] Another possible explanation for anemia in mHSPC patients is bone marrow infiltration. In this study, patients in the anemia-ABI group had a significantly worse EOD than those in the non-anemia-ABI group. Additionally, our study demonstrated that EOD ≥ 3 was the strongest factor of pretreatment anemia in the entire cohort (Fig. S2B). Anemia due to replacement of normal bone marrow with cancer cells is termed leucoerythroblastic anemia, [17] which is observed in approximately 30% of patients with metastatic CRPC. [20] These findings suggest that anemia among advanced PC patients may reflect cancer cachexia and/or disease aggressiveness.

The relationship between anemia and prognosis in patients with metastatic PC is debatable. A meta-analysis demonstrated that of the mHSPC patients in the ADT/CAB group, those with anemia had a significantly shorter PFS than those without anemia. [8] Tumor hypoxia caused by anemia and ADT may explain the relationship between anemia and poor prognosis in metastatic PC. Cancer-associated systemic anemia can cause decreased oxygen transport capacity of the blood, which contributes to hypoxia in the tumor microenvironment. [21,22] Hypoxia may decrease tumor control through the induction of hypoxia-inducible factor 1α (HIF-1α). [23] HIF-1α has been identified to activate HIF-1β to form a transcription factor complex that regulates the expression of several genes, such as vascular endothelial growth factor and glucose transporters, which is strongly associated with angiogenesis and tumor growth.[24,25] Tumor hypoxia is often associated with treatment resistance in other cancers [26]. Tumor hypoxia in PC cell was associated with clinical stage and biochemical recurrence in locally advanced prostate cancer. [27,28] Furthermore, ADT may accelerate hypoxia in PC cells, which ultimately results in CRPC. [29] Although the relationship between tumor hypoxia and responsiveness to ADT in mHSPC remains unclear, we speculated that poor clinical outcomes of mHSPC patients with anemia might be related with tumor hypoxia. Therefore, improvement in the prognosis of mHSPC patients with anemia is a key issue for clinicians.

Optimal selection of upfront intensive therapies for mHSPC patients with anemia must be carefully considered. Patients with anemia and/or malnutrition (cancer cachexia) are believed to be intolerant to chemotherapies.[30] In this regard, patients with anemia and/or malnutrition should be treated with upfront ABI therapy rather than upfront docetaxel. Indeed, the rate of AE-related discontinuation of ABI among patients with anemia was not very high in this study. However, our results implied that the efficacy of

upfront ABI therapy might be limited in mHSPC patients with anemia. As no clinical trial of ARTAs focused on the impact of anemia on prognosis, further studies are necessary to confirm our findings. Careful selection for upfront ABI therapy might be necessary in mHSPC patients with anemia.

This study included a small sample size and a short-term follow-up period, which precluded a definitive conclusion regarding the long-term survival benefit. We did not obtain a full dataset on nutritional status and other immeasurable confounding factors. In this study, we therefore had to exclude 377 (52%) patients who received ADT/CAB due to lacking essential data, which resulted in major selection bias. Our results may not be applicable to other countries because of racial and regional differences. Despite these limitations, we revealed the prognostic significance of pretreatment anemia among mHSPC patients who received upfront ABI therapy.

Conclusion

The upfront ABI therapy significantly improved the PFS of mHSPC patients, especially those without anemia. However, its efficacy in patients with anemia might be limited. Studies with a larger sample size and longer follow-up are needed to confirm our results.

Declarations

Ethics approval and consent to participate

This retrospective study was performed according to the ethical standards of the Declaration of Helsinki and was further approved by the ethics review board of the Hirosaki University School of Medicine (authorization number: 2019–094). Pursuant to the provisions of the ethics committee and the ethic guideline in Japan, written consent was not required in exchange for public disclosure of study information in the case of retrospective and/or observational study using a material such as the existing documentation.

Consent for publication

Not applicable

Competing interests

All authors have no conflicts of interest to declare.

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Author contributions

(1) Conception and design: Shingo Hatakeyama, Shintaro Narita; (2) Acquisition of data: All authors; (3) Data analysis and interpretation: Teppei Okamoto, Shingo Hatakeyama, Chikara Ohyama; (4) Manuscript writing: Teppei Okamoto, Shingo Hatakeyama; (5) Final approval of manuscript: All authors.

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Availability of data and materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

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Tables

Due to technical limitations, table pptx is only available as a download in the Supplemental Files section.

Figures

Figure 1

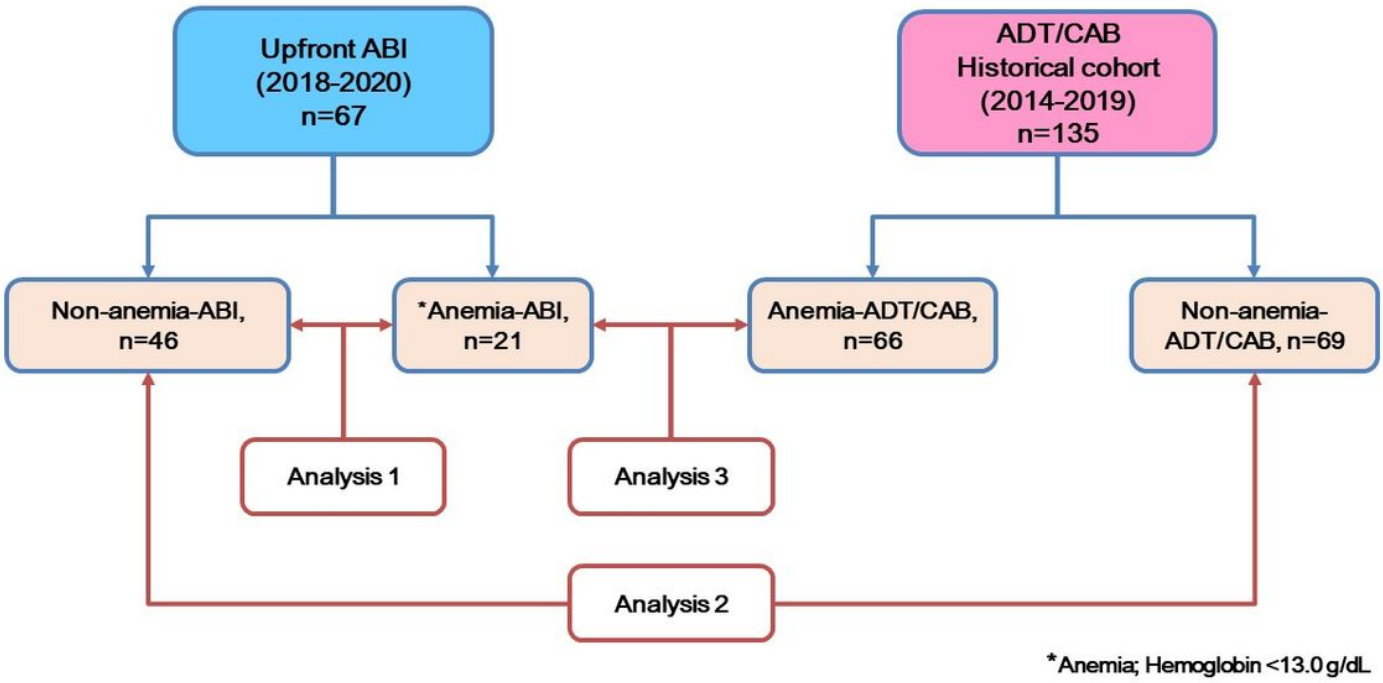

Figure 1

Patient evaluation Patients with high tumor burden (CHAARTED high-volume and/or LATITUDE high-risk) were evaluated in this study. We identified 67 and 135 patients in the ADT/CAB and upfront groups, respectively. We divided the patients according to the presence of pretreatment anemia into the non-anemia-ABI, anemia-ABI, non-anemia-ADT/CAB, and anemia-ADT/CAB groups.

Figure 2

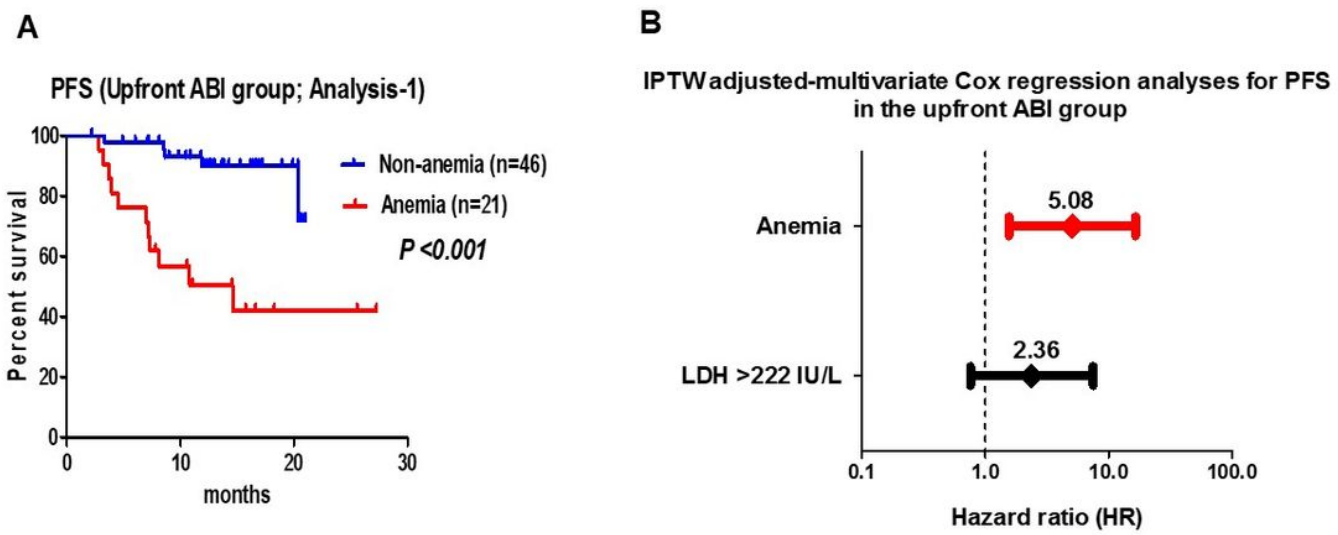

Figure 2

Comparison of clinical progression (Analysis-1) (A) PFS between patients in the anemia-ABI and non-anemia-ABI groups (Analysis-1) (median, not reached vs. 15 months; P <0.001). (B) IPTW adjusted-multivariate logistic regression analyses for PFS in the upfront ABI group (adjustments for age, ECOG PS, initial PSA, Gleason score, visceral metastasis, EOD, and ALP and LDH/Hb levels). Anemia (HR, 5.08; 95% CI, 1.56–16.5 P = 0.007). LDH level >222 IU/L (HR, 2.36; 95% CI, 0.76–7.49 P = 0.142).

Figure 3

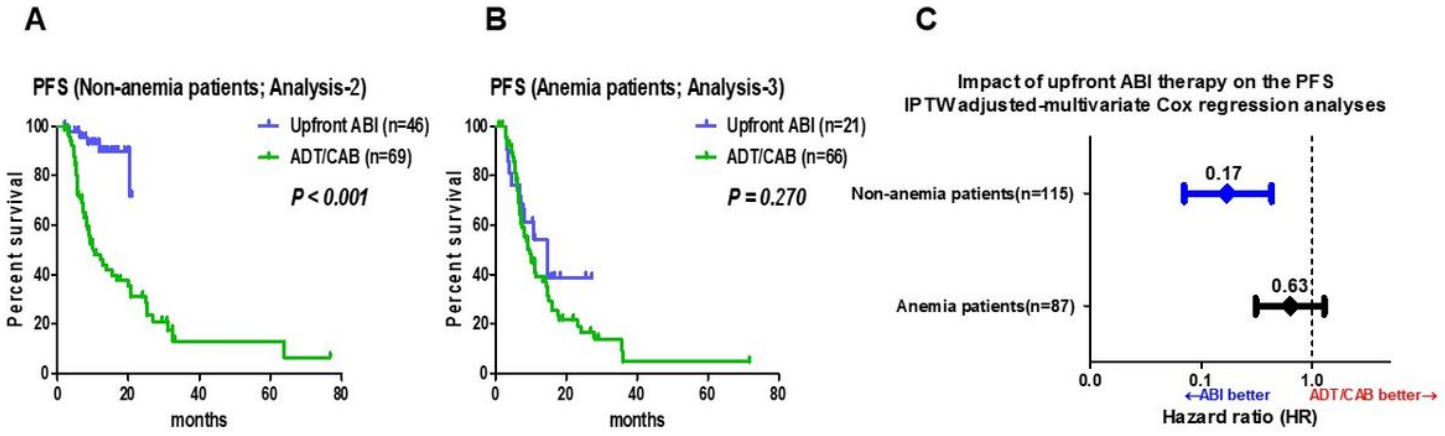

Figure 3

Comparison of clinical progression (Analysis-2, 3) (A) PFS between patients in the non-anemia-ABI and non-anemia-ADT/CAB groups (Analysis-2) (median, not reached vs. 10.5 months; P <0.001). (B) PFS between patients in the anemia-ABI and anemia-AD/CAB groups (Analysis-3) (median, 14 vs. 10 months; P = 0.270). (C) IPTW adjusted-multivariate Cox regression analyses for PFS of upfront ABI (adjustment for age, ECOG PS, initial PSA, Gleason score, visceral metastasis, EOD, and ALP and LDH levels). Top for the non-anemia patients; (HR, 0.17; 95% CI, 0.07–0.43; P = 0.003). Bottom for the anemia patients; (HR, 0.63; 95% CI, 0.31–1.28; P = 0.206).

Supplementary Files

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