A prognostic model for stratifying clinical outcomes in chemotherapy-naive metastatic castration-resistant prostate cancer patients treated with abiraterone acetate

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Abstract

Introduction: Recently, a prognostic index including six risk factors (RFs) (unfavourable ECOG performance status [PS], presence of liver metastases, short response to luteinizing hormone-releasing hormone [LHRH] agonists/antagonists, low albumin, increased alkaline phosphatase [ALP] and lactate dehydrogenase [LDH]) was developed from the COU-AA-301 trial in post-chemotherapy metastatic castration-resistant prostate cancer (mCRPC) patients treated with abiraterone acetate. Our primary objective was to evaluate this model in a cohort of chemotherapy-naive mCRPC patients receiving abiraterone.
Methods: We identified 197 chemotherapy-naive patients who received abiraterone at six BC Cancer Agency centres and who had complete information on all six RFs. Study endpoints were prostate-specific antigen (PSA) response rate (RR), time to PSA progression, time on treatment, and overall survival (OS). PSA RR and survival outcomes were compared using X^2 test and log-rank test. Multivariable Cox proportional hazard analysis was performed to identify RFs independently associated with OS.
Results: Patients were classified into good (0–1 RFs), intermediate (2–3 RFs), and poor (4–6 RFs) prognostic groups (33%, 52%, and 15%, respectively). For good, intermediate, and poor risk patients, PSA RR (≥50% decline) was 60% vs. 42% vs. 40% (p=0.05); median time to PSA progression was 7.3 vs. 5.3 vs. 5.0 months (p=0.02); and median OS was 29.4 vs. 13.8 vs. 8.7 months (p<0.0001).

Conclusions: The six-factor prognostic index model stratifies clinical outcomes in chemotherapy-naive mCRPC patients treated with abiraterone. Identifying patients at risk of poor outcomes is important for informing clinical practice and clinical trial design.

Introduction

The therapeutic landscape for metastatic castration-resistant prostate cancer (mCRPC) has rapidly evolved in recent years with many new agents demonstrating a benefit in overall survival (OS).[1] One of these agents is abiraterone acetate (abiraterone), an orally available inhibitor of CYP17 that blocks adrenal and intra-tumoural androgen synthesis. Abiraterone confers an OS advantage both as first-line therapy in chemotherapy-naïve patients as well as in the post-docetaxel chemotherapy setting.[2,3] However, despite its efficacy, outcomes with abiraterone are variable and not all patients derive benefit from treatment. Thus, there is an urgent need for a practical clinical tool able to stratify patients accurately into distinct prognostic categories.
In a recent post-hoc analysis of the COU-AA-301 study, a prognostic model was developed for predicting OS in post-docetaxel patients treated with abiraterone.[4] This model comprises six risk factors (RFs) linked to poor survival: ECOG PS ≥ 2, liver metastases, time from initiation of androgen deprivation therapy (ADT) to initiation of abiraterone ≤ 36 months, low albumin ($\leq$ 4g/dl), LDH above upper limit normal (ULN) and alkaline phosphatase (ALP) above ULN. Classification of the COU-AA-301 trial population into good (0-1 RFs), intermediate (2-3 RFs) and poor (4-6 RFs) risk groups revealed OS of 21.3 months, 13.9 months (Hazard Ratio (HR) 2.3) and 6.1 months (HR 6.2) respectively. This model was subsequently validated in a population-based cohort of post-chemotherapy mCRPC patients treated with abiraterone.[5] The utility of this model in chemotherapy-naïve patients has also been examined in a preliminary analysis incorporating only 64 patients.[6]

The COU-302 trial which evaluated abiraterone in chemotherapy-naïve patients with CRPC showed a significantly longer OS than the post-chemotherapy COU-301 trial (34.7 vs 15.8 months),[3,7] and the performance of our 6-factor prognostic model in that setting is currently unknown. The aim of our study was to determine whether this prognostic model determines clinically relevant prognostic groups in chemotherapy-naïve patients treated with abiraterone in a real-world setting across six cancer centres in British Columbia, Canada.

Methods

Patient population

The BC Cancer Agency (BCCA) consists of six distinct centres and coordinates cancer care delivered throughout British Columbia, Canada. The Cancer Registry at BCCA was reviewed for chemotherapy-naïve mCRPC patients who started abiraterone between July 2009 and October 2014. Patient demographics, prior treatments, clinico-pathological characteristics and outcomes on abiraterone were documented from medical records of each patient. Only patients with available data for all 6 RFs in the prognostic index were included in this study. Research ethics board approval was obtained prior to commencing this study.

Outcome measures

Patients were classified into good (0-1 RFs), intermediate (2-3 RFs) and poor (4-6 RFs) risk groups. The following endpoints were determined for each patient: confirmed PSA response rate (PSA decline ≥ 50% from baseline maintained for ≥ 3 weeks), time to PSA progression (Prostate Cancer Working Group 2 (PCWG2) criteria),[8] time on treatment (time from initiation of abiraterone to discontinuation for any reason) and overall survival (OS) (time from initiation of abiraterone to death of any cause or censoring on November 1st, 2016). Reasons for discontinuation of abiraterone were recorded as follows: Radiographic (Prostate Cancer Working Group 2 (PCWG2) criteria), biochemical (PCWG2 criteria) or clinical (worsening disease-related symptoms requiring a change in anti-neoplastic therapy or a decrease in ECOG PS of ≥ 2 levels).[9,10]

Development of the prognostic model

Construction of the six-factor prognostic model has been previously described.[4,11] In brief, the following steps were involved: i) key clinico-pathological factors were identified and dichotomised for high/low values as necessary; ii) association between baseline clinico-pathological factors and OS was investigated using a univariate Cox proportional hazards model; iii) factors that were significant on univariate analysis were incorporated into a multivariate Cox proportional hazards regression model (step-wise procedure); iv) factors that were significant on multivariate analysis were incorporated into the final model, which was then subjected to validation by a bootstrapping approach; v) the C-index was used to determine accuracy of the model, which comprised six separate RFs; and vi) patients were then classified into risk groups based on the number of baseline RFs with median OS calculated for each risk group.

Statistics

Univariate analysis examining association between prognostic group and PSA response was performed using X^2 test. Survival outcomes were estimated using the Kaplan-Meier method. Log-rank test was performed to assess survival differences between groups. Multivariable analysis using Cox proportional hazards model was performed to identify RFs independently associated with OS. Statistical analysis was performed using SPSS® v.14.0 software. To determine the model's accuracy, the c-index was calculated for time on treatment, time to PSA progression and OS.

Results

Patient population

Two hundred and forty-six chemotherapy-naïve patients who received abiraterone from July 2009 (when abiraterone became available) until October 2014 were identified. One hundred and ninety-seven patients were included for this analysis as they had available data for each of the 6 RFs comprising the six-factor prognostic model. Patient characteristics at initiation of abiraterone are listed in Table 1. The median age at start of abiraterone was 80 years

(interquartile range 71-84), 38% of patients had ECOG PS of 2 or higher and 3% had liver metastasis. Overall, 33% (65/197), 52% (102/197) and 15% (30/197) of patients were classified as good, intermediate and poor prognosis respectively as per the prognostic index.
Reasons for abiraterone discontinuation (more than one could apply) were clinical progression (36%), PSA progression (67%), radiologic progression (33%) and toxicity (8%), while 5.5% (11/197) of patients were still on abiraterone as of November 1st, 2016. Post-abiraterone systemic treatment was administered to 54% of patients (100/186).

PSA response

Confirmed PSA declines ≥ 90%, ≥ 50% and ≥ 30% were seen in 13% (26/197), 48% (94/197) and 51% (100/197) of patients respectively. All three levels of PSA decline were significantly more frequent in good versus intermediate and poor-risk patients (Table 2). Only ECOG PS was significantly associated with PSA decline ≥ 50% on univariate analysis (X^2 test).

Survival endpoints

For the overall cohort, median time to PSA progression, median time on treatment and median OS was 6.5 months (95% CI 5.6-8.0), 7.4 months (95% CI 6.0-8.5) and 15.7 months (95% CI 12.9-18.9) respectively. As shown in Table 2, time to PSA progression and time on treatment were significantly longer in the good prognosis group versus the intermediate and poor risk groups ($P = 0.02$ and $P < 0.0001$ respectively; log-rank). Hazard ratios for each group are shown in Table 3. OS was significantly better in the good prognosis group compared with the intermediate and poor prognostics groups (29.4 vs 13.8 vs 8.7 months, respectively, $P < 0.0001$). Kaplan-Meier curves are shown in Figure 1. On multivariable analysis incorporating the 6 RFs from the prognostic index, ECOG PS ($P < 0.0001$), liver metastases ($P = 0.0008$), time from initiation of ADT to abiraterone ≤ 36 months ($P = 0.02$) and serum ALP ($P < 0.0001$) were confirmed as independent prognostic factors for OS, whereas serum albumin and serum LDH did not meet statistical significance (Table 4). The predictive accuracy of our model as measured by the c-index was 0.79, 0.68 and 0.66 for OS, time on treatment and time to PSA progression, respectively.

Discussion

Although abiraterone has proven efficacy in chemotherapy-naïve patients with mCRPC, treatment outcomes are variable and difficult to predict at an individual patient level. Recently, a prognostic model for OS in patients receiving abiraterone after prior docetaxel chemotherapy was developed based on data from the COU-AA-301 phase III trial, and subsequently validated in a population based cohort.[4,5] In the present study, we confirm the performance and discriminatory power of this model in a large, unselected and sequential cohort of chemotherapy-naïve mCRPC patients treated with abiraterone. Our real-world population differed significantly from patients in the COU-AA-302 study which established the efficacy of abiraterone in chemotherapy-naïve patients. We included patients with poor performance status, significant pain symptoms and visceral metastasis, all of which were exclusion criteria for the COU-AA-302

study. This is reflected in the difference between the median overall survival of our cohort (15.7 months) compared to the median overall survival observed in the COU-AA-302 study (34.7 months).[3] In addition, a lower proportion of our patients had low risk versus intermediate or high risk prognostic scores (33% vs 67% respectively), compared to the COU-AA-301 study (46% vs 53%).[4] This also further emphasizes the applicability and generalizability of the prognostic model to the broader patient population treated with abiraterone.

We observed a clear and statistically significant difference in OS between good, intermediate and poor-risk patients and confirmed that presence of liver metastases, time from initiation of ADT to initiation of abiraterone ≤ 36 months, serum ALP ≥ ULN and ECOG PS ≥ 2 are independent prognostic factors. Interestingly, serum LDH and serum albumin showed no independent prognostic value for OS, although this is likely due to the limited sample size of our study. These results contrast with those of an external validation of the prognostic index performed by Ravi *et al* at Royal Marsden.[6] In their cohort of 64 chemotherapy-naïve patients, low albumin was the only independent factor predicting OS in multivariable analysis. However, this was a relatively small validation cohort which included only one chemotherapy-naïve patient with poor prognosis disease, and differed from our cohort in that no chemotherapy-naïve patients with ECOG PS ≥ 2 were included whereas these patients comprised 38% of our cohort. The different cohort characteristics and larger sample size may also account for the better predictive power of the model in our study as Ravi *et al* observed a relatively modest OS difference of 10 months between good and intermediate/poor-risk patients.

There is strong evidence from other studies supporting the prognostic value of the clinical factors included in our model. A prognostic nomogram was developed and validated by Halabi *et al* from two randomized controlled trials of first-line docetaxel for mCRPC.[12] Their analysis also showed that ECOG PS, site of metastasis, LDH, albumin, hemoglobin and ALP predict OS on multivariable analysis, in addition to opioid analgesia use and PSA. However, they did not test the prognostic significance of duration of primary ADT when building their model, and its performance in the setting of first-line abiraterone has not been verified. In a study of 161 patients treated with abiraterone, McKay *et al* demonstrated that duration of primary ADT > 12 months and no prior docetaxel chemotherapy were independently associated with a longer time on abiraterone.[13] In addition, a recent meta-analysis evaluating the impact of site of metastasis on overall survival in men with CRPC showed that liver metastasis predicted worse OS compared to bone metastasis and lymph node only metastasis (13.5 vs 21.3 vs 31.6 months, respectively).[14] In addition to OS, we observed that the 6-factor prognostic index model is predictive of time to PSA progression, PSA response and time on treatment in chemotherapy-naïve patients treated with abiraterone. The use of PSA parameters as a surrogate endpoint for OS in CRPC has generated considerable discussion and controversy. However recently, Xu *et al* constructed a biomarker-survival modelling framework to explore the relationship between PSA kinetics (including time to PSA progression and PSA response) and OS in metastatic CRPC patients following administration of abiraterone.[15] In their analysis, which was based on data from the COU-AA-301 and COU-AA-302 trials, PSA kinetics were highly associated with OS in both

chemotherapy-experienced patients and chemotherapy-naïve patients. The authors concluded that PSA kinetics should be considered as surrogate end points of clinical benefit in abiraterone-treated patients regardless of chemotherapy treatment.[15] Our observation that the prognostic model predicted for both PSA response and OS in the present cohort is in accordance with this data. Our model was also predictive for time on treatment, a useful surrogate in the real-world setting for the duration of clinical benefit on treatment and an important endpoint, as highlighted in the updated recommendations on trial design and objectives from the Prostate Cancer Working Group 3.[16] These findings demonstrate that our model is predictive of outcomes on abiraterone and thus may be valuable in selecting patients likely to benefit from first-line abiraterone, and identifying those for whom alternate treatments could be considered, such as first-line chemotherapy or clinical trials.

A key strength of the 6-factor prognostic index model is that it is a pragmatic tool for risk stratification utilising easily available (and inexpensive) clinical parameters. Nevertheless, integration of this model with emerging molecular biomarkers including androgen receptor (AR) splice variants, circulating tumour DNA (ctDNA) and circulating tumour cells (CTCs) will be important. AR splice variant 7 (ARv7) detection in CTCs was recently proposed as a mechanism driving primary resistance to enzalutamide and high levels of full-length AR mRNA and presence of ARv7 have been shown to correlate with PSA progression-free survival and OS on abiraterone or enzalutamide.[17,18] Recent evidence has revealed that structural variants of the AR gene are associated with the presence of AR splice variants, and may also be important drivers of treatment resistance.[19] In addition, AR gene aberrations (copy number change and/or mutations) in pre-treatment ctDNA have been linked to adverse outcomes in mCRPC patients commencing abiraterone and enzalutamide.[20,21] A biomarker panel incorporating CTC enumeration and LDH was also recently shown to predict OS in a post-hoc analysis of the COU-AA-301 trial.[22]
The present study has various limitations. These include its retrospective design, being limited to a single province in Canada and the relatively small sample size. We could not assess radiological response to treatment since imaging was not consistently performed. Data on radiographic progression-free survival were not analysed due to wide variation in follow-up including timing of imaging.

Conclusion

In conclusion, we observe that the 6-factor prognostic index model provides reliable risk stratification for chemotherapy-naïve patients receiving abiraterone by predicting PSA response, time to PSA progression, time on treatment and OS. ECOG PS, liver metastases, time from androgen deprivation therapy (ADT) to initiation of abiraterone ≤ 36 months and serum ALP were confirmed as independent risk factors for poor OS in the pre-chemotherapy setting. Due to its predictive capability, we suggest that incorporating the prognostic model in clinical practice and future trials assessing the use of novel hormonal agents and cytotoxics will allow improved risk stratification and optimized treatment selection.

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Figures and Tables

Fig. 1. Kaplan-Meier curves for: ***(A)*** overall survival; ***(B)*** time on treatment ; and ***(C)*** PSA progression for good, intermediate, and poor prognosis groups.

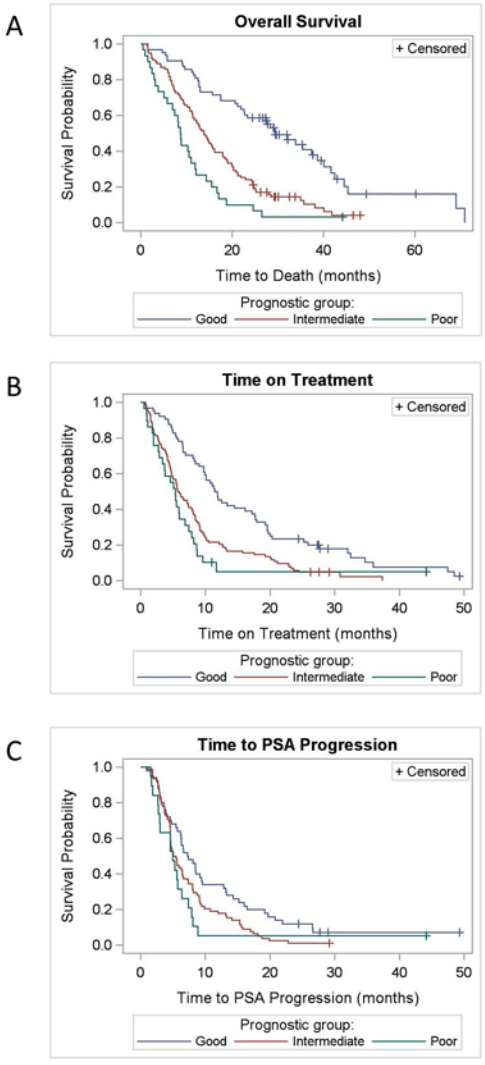

Table 1. Baseline characteristics at initiation of abiraterone acetate (n=197)	
Characteristic	
Age	
Median (IQR)	80 (71–84)
Gleason score	
4–5	5 (3)
6–7	49 (25)
8–10	109 (55)
Unknown	34 (17)
Disease sites, n (%)	
Bone	149 (76)
Lymph node	58 (29)
Liver	5 (3)
Time since commencing ADT	
Median (months, IQR)	47 (22–93)
ECOG PS, n (%)	
0–1	122 (62)
≥2	75 (38)
Bone pain[a], n (%)	
Yes	65 (33)
No	129 (66)
Disease progression, n (%)	
PSA	175 (89)
Clinical	105 (53)
Radiographic	99 (50)
Laboratory	
LDH (median, U/L) (IQR)	234 (179–361)
Elevated (≥ULN), n (%)	55 (28)
ALP (median, U/L) (IQR)	113 (80–221)
Elevated (≥ULN), n (%)	69 (35)
Albumin (median, U/L) (IQR)	38 (35–41)
Low (<4g/dl), n (%)	130 (66)
Hemoglobin (median, U/L) (IQR)	123 (111–132)
Low (<100), n (%)	22 (11)

[a]Bone pain defined as requiring radiotherapy and/or opioid analgesia within 28 days of commencing abiraterone. ADT: androgen-deprivation therapy (LHRH agonist or antagonist for metastatic or relapse disease); ECOG PS: Eastern Cooperative Group Performance Status; IQR: interquartile range.

Table 2. PSA response, time on treatment, time to PSA progression, and overall survival on abiraterone acetate stratified by prognostic group				
Parameter	**Good prognosis (0–1 RF) (n=65)**	**Intermediate prognosis (2–3 RF) (n=102)**	**Poor prognosis (4–6 RF) (n=30)**	**p**
PSA decline[a]				
Decline ≥90, n (%)	14 (22)	11 (11)	1 (3)	0.04
Decline ≥50, n (%)	39 (60)	43 (42)	12 (40)	0.05
Decline ≥30, n (%)	40 (62)	46 (45)	14 (47)	0.10
Time on treatment				
Median (month, 95% CI)	11.6 (9.7–17.2)	5.8 (4.8–7.8)	5.3 (2.9–6.9)	<0.0001
Time to PSA progression[b]				
Median (months, 95% CI)	7.3 (5.7–9.4)	5.3 (4.6–6.5)	5.0 (2.8–6.4)	0.02
Overall survival[c]				
Median (months, 95% CI)	29.4 (22.6–38.7)	13.8 (11.4–16.1)	8.7 (5.8–11.9)	<0.0001

[a]PSA decline confirmed ≥3 weeks later; [b]PCWG2 criteria; [c]from time of commencing abiraterone. CI: confidence interval; PSA: prostate-specific antigen; RF: risk factors (including: ECOG performance status ≥ 2; liver metastases; time on androgen-deprivation therapy to initiation of abiraterone ≤36 months; low albumin (<4g/dl); high LDH (>upper limit normal); and high ALP (>upper limit normal).

Table 3. Hazard ratios for time on treatment, time to PSA progression, and overall survival stratified by prognostic group			
	Hazard ratio[a]		
Parameter	**Good (0-1 RF)**	**Intermediate (2-3 RF)**	**Poor (4-6 RF)**
Time on treatment (95% CI)	-	2.0 (1.4–2.8)	2.7 (1.7–4.3)
Time to PSA progression[b] (95% CI)	-	1.5 (1.1–2.2)	2.0 (1.1–3.4)
Overall survival[c] (95% CI)	-	2.5 (1.7–3.6)	4.4 (2.7–7.1)

[a]Relative to good prognosis group; [b]PCWG2 criteria; [c]from time of commencing abiraterone. CI: confidence interval; PSA: prostate-specific antigen; RF: risk factors (including: ECOG performance status ≥2; liver metastases; time on androgen-deprivation therapy to initiation of abiraterone ≤36 months; low albumin (<4g/dl); high LDH (>upper limit normal); and high ALP (>upper limit normal).

Table 4. Multivariate analysis examining association between baseline clinico-pathological factors and overall survival in chemotherapy-naive mCRPC patients treated with abiraterone

Characteristic	HR	95% CI	p
Time on ADT	1.5	1.1–2.1	0.02
ECOG PS	2.2	1.6–3.1	<0.0001
Serum LDH	1.2	0.8–1.7	0.39
Serum ALP	2.1	1.5–3.0	<0.0001
Liver metastases	5.0	1.9–12.7	0.0008
Serum albumin	1.0	0.7–1.4	0.88

ADT: androgen-deprivation therapy; ALP: alkaline phosphatase; CI: confidence interval; HR: hazard ratio; LDH: lactate dehydrogenase; mCRPC: metastatic castration-resistant prostate cancer.