Evaluation of primary androgen deprivation therapy in prostate cancer patients using the J–CAPRA risk score

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Purpose: To determine the influence of maximal androgen blockade (MAB) and non-MAB hormonal therapy with an luteinizing hormone releasing hormone (LHRH) analog on overall survival of prostate cancer patients in the Japan Study Group of Prostate Cancer (J-CaP) registry according to risk, as assessed using the novel J-CAPRA risk instrument. To undertake a multivariate analysis combining J-CAPRA risk score, type of hormonal therapy and comorbidities, in order to assess their impact on overall survival.
Methods: The J-CaP database includes men in Japan diagnosed with any stage of prostate cancer between 2001 and 2003 and treated with primary androgen deprivation therapy (PADT), as monotherapy or in combination. A total of 26,272 men were enrolled and of these 19,265 were treated with PADT. This analysis was undertaken using the latest data set (30 April, 2010) including a total of 15,727 patients who received PADT and had follow-up data for periods ranging from 0 to 9.2 years.
Results: MAB for prostate cancer patients with intermediate- or high-risk disease has a significant benefit in terms of overall survival compared with LHRH analog monotherapy or surgical castration alone. Better results may be achieved in older (≥ 75 years) patients. Patient comorbidities are an important factor in determining overall survival, notably in older patients, and should be considered when selecting therapy.
Conclusions: Based on large-scale registry data, this report is the first to analyze the outcomes of MAB therapy in patients with prostate cancer at a wide range of disease stages. MAB therapy may provide significant survival benefits in intermediate- and high-risk patients.

Keywords: Prostate neoplasms, Maximal androgen blockade, Overall survival, Primary androgen deprivation therapy, Risk scoring

INTRODUCTION

Prostate cancer is recognized as a hormone-dependent condi- tion whereby tumour growth is stimulated by endogenous cir- culating androgens. Therefore one of the standards of care for advanced, metastatic disease is primary androgen deprivation

therapy (PADT) which can be achieved by either surgical castration or by medical castration using a luteinizing hormone releasing hormone (LHRH) analog. Around 95% of endogenous testosterone is produced by the testes and while castration eliminates this source of the hormone, there is still a secondary source from the adrenal glands that is available to stimulate tumour growth.

The concept of maximal androgen blockade (MAB), which describes the combination of an antiandrogen and either an LHRH analog or surgical castration, was therefore proposed as a therapeutic option, the aim being to eliminate both testicular and adrenal androgens simultaneously. As with every proposed therapeutic regimen, it is important that clinical evidence is generated to demonstrate its efficacy and safety in patients before it is recommended in treatment guidelines and adopted into routine clinical practice.

In the case of MAB, since its initial proposition over 20 years ago there has been considerable debate regarding its relative benefits compared with LHRH monotherapy or castration, and these deliberations have been the subject of recent reviews [1,2]. Results from randomized clinical trials (RCTs) have often provided equivocal results and reports of the benefits of MAB in terms of safety, quality of life, survival and cost effectiveness have been limited [2].

Recently the results of a Phase III, prospective RCT of MAB in Japanese patients with advanced prostate cancer have provided us with additional evidence of the benefits of MAB over LHRH analog monotherapy in terms of superior antitumor response, time to treatment failure, disease progression and overall survival, achieved without any reduction in tolerability [3-5].

Patient registries are also a valuable source of data on therapeutic efficacy and patient outcomes. In view of the extensive use of the different forms PADT, including MAB, for the treatment of prostate cancer in Japan, in 2001 the Japan Study Group of Prostate Cancer (J-CaP Study Group; http://www.j-cap.net) supported by the Japan Kidney Foundation and authorized by the Japanese Urological Association (JUA), commenced a study to gather information about hormone therapy administered to Japanese patients living in Japan and to analyze the outcomes of treatment. The result was the J-CaP registry, a large, multicenter, population-based database of men newly starting PADT for prostate cancer.

The rationale for development of the J-CaP database and an interim analysis of the registration status of the patients and their background variables was reported in 2003 [6] and more recently treatment patterns with PADT have been reported along with an interim analysis of prognosis [7]. Within the J-CaP database 59.0% of all patients received MAB therapy and these regimens were most often administered to patients who were considered to be at high risk of disease progression [7].

An exploration of the influence of the different types of hormonal therapy on disease outcomes concluded that MAB therapy was possibly superior to LHRH monotherapy in terms of progression-free survival (PFS) for stage II and III prostate cancer and overall survival for stage III and IV prostate cancer however the number of events was small and therefore did not allow any firm conclusions to be reached at that stage [7]. More recent follow-up data for 15,461 prostate cancer patients within the J-CaP database found that MAB therapy may be superior to LHRH analog monotherapy in terms of PFS for clinical stage II disease. In addition, disease progression appears to be inhibited in patients with clinical stage II and III disease receiving MAB therapy, and they were found to have a life expectancy similar to that of the normal population [8].

Risk stratification of patients within the J-CaP population is not straightforward as there are very few published risk instruments that have been validated for use in the Japanese population and that are suitable for use with patients at all disease stages [9]. A novel risk instrument was recently developed and validated for patients undergoing PADT, named 'J-CAPRA', details of which have been published previously [10]. J-CAPRA was designed and validated to be specifically applicable to patients receiving PADT, and more relevant than existing instruments to the high-risk patients that form a large proportion of the J-CaP database.

This paper reports the results of an analysis of the most recent follow-up data from the J-CaP database to explore the influence of MAB and non-MAB hormonal therapy with an LHRH analog on overall survival of prostate cancer patients according to their J-CAPRA risk score. It also describes the results of a multivariate analysis combining J-CAPRA score, type of hormonal therapy, and different comorbidities, and their impact on overall survival.

MATERIALS AND METHODS

The J-CaP database includes men in Japan diagnosed with any stage of prostate cancer between 2001 and 2003 and treated with androgen deprivation therapy (ADT), as monotherapy or in combination. Three hundred eighty-four institutions contributed patients, comprising approximately 50% of all men diagnosed in Japan during the accrual period, and nearly 95% of those treated with PADT. Of the patients included in the database, 18.5% were treated in academic medical centers, and the remainder in the community.

TNM stage (1997) was reported directly by participating clinicians however detailed biopsy data were not included. Urologists at participating institutions report follow-up findings every 3 months on an ongoing basis, including information on additional treatments, progression, and all-cause mortality.
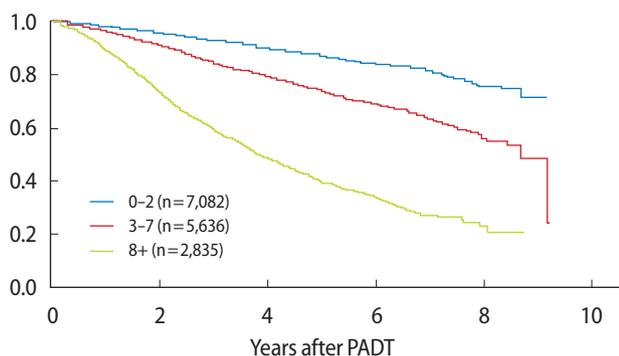
A total of 26,272 men were enrolled in J-CaP; of these 19,265 were treated with PADT. Additional information regarding J-CaP has been published previously [6,7]. This current analysis was undertaken using the latest data set (as of 30 April, 2010) for 15,727 prostate cancer patients treated with PADT who had sufficient pathological and clinical data including follow-up data.

Data for overall survival were stratified according to J-CAP-RA risk criteria [10] and by type of hormonal therapy (MAB or non-MAB) received, and the patient's age. Multivariate analyses were also performed to investigate the influence of various factors—J-CAPRA score, type of hormonal therapy, and different comorbidities—on overall survival. Statistical analysis was performed using a proportional hazards model (Cox regression). Prognosis analyses were performed using Kaplan-Meier methods. Survival analysis was tested using the log-rank test. Microsoft Excel was employed for depicting survival curves.

All statistical analyses were performed using JMP ver. 8 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Within the J-CaP database, of the 19,277 patients who initially received PADT after diagnosis of prostate cancer, 11,372 patients (59.0%) of all cases received MAB therapy. This latest dataset includes a total of 19,277 patients who received PADT and

had follow-up data for periods ranged from 0 to 9.2 years. In total there were 3,399 events comprising 1,691 cancer deaths and 1,708 deaths due to other causes. A total of 2,549 patients were missing data for their Gleason score, therefore the latest dataset with J-CAPRA scores includes 15,727 patients.

1. Age of patients

In terms of age distribution, of the 15,727 patients who received PADT and were included in the analysis, around 48% of were 75 years of age or over. Analysis of J-CAPRA risk category (low, 0–2; intermediate, 3–7; high, 8+) by age group (≤65,

Fig. 2. Overall survival according to J-CAPRA risk score for three age groups of patients (≤65 [A], 66–75 [B], and >75 years of age [C]) who received primary androgen deprivation therapy (PADT) (P<0.0001). J-CAPRA score: low (0–2, blue), intermediate (3–7, red), high (8+, green).
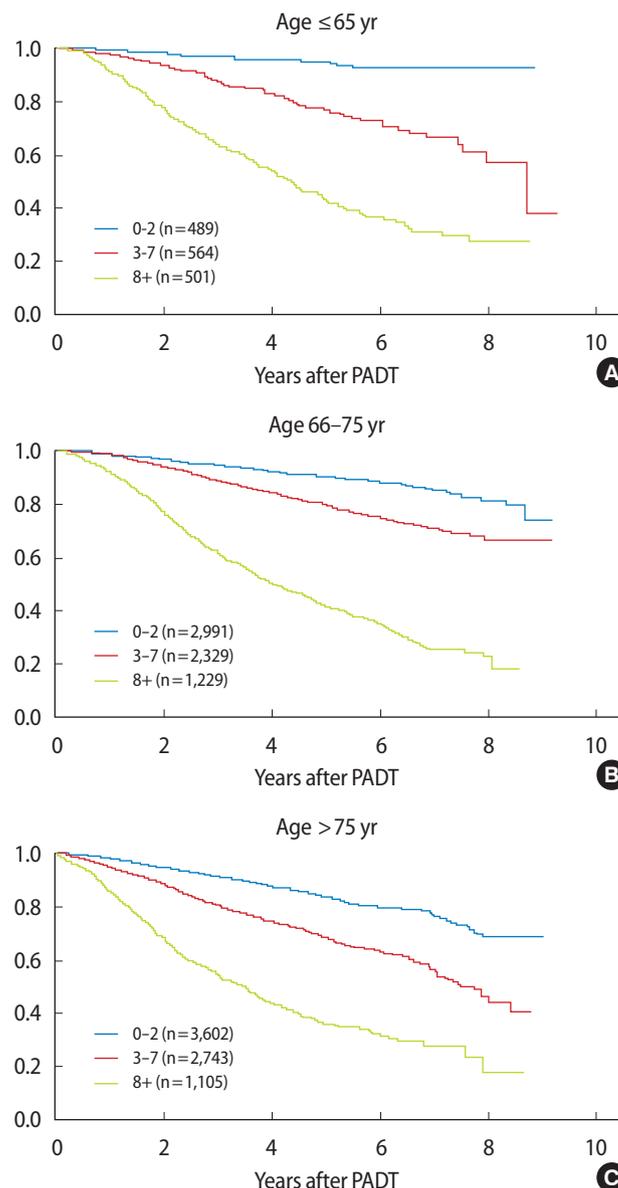
Fig. 1. Overall survival according to J-CAPRA risk score for all patients who received primary androgen deprivation therapy (PADT) and were included in the analysis (n=15,553, P<0.001). J-CAPRA score: low (0–2, blue), intermediate (3–7, red), high (8+, green).

66–75, >75 years of age) found a higher proportion of low-risk patients in the older age category (48%) compared to the younger two age categories (45% and 31%, respectively).

2. Overall survival according to J-CAPRA risk score – all patients

Of the 15,553 patients included in this analysis who received PADT and had follow-up data available, 7,082 patients had a low J-CAPRA risk score, while 5,636 and 2,835 patients had intermediate and high J-CAPRA risk scores, respectively (Fig. 1). Analysis of the overall survival of all patients who received PADT according to their J-CAPRA risk score found that increasing J-CAPRA risk score was associated with reduced overall survival regardless of age (Fig. 1); $P < 0.0001$ (overall), $P < 0.0001$ (low risk vs. intermediate risk) and $P < 0.0001$ (intermediate risk vs. high risk).

3. Overall survival according to J-CAPRA risk score and age

Overall survival according to J-CAPRA risk score for three age groups of patients (≤65, 66–75, and >75 years of age) who received PADT is shown in Fig. 2. When analyzed according to age category, it was found that within each age cohort increasing J-CAPRA risk score was associated with reduced overall survival ($P < 0.0001$). For each J-CAPRA risk group there was a slight tendency to reduced overall survival with increasing age. Overall survival estimates are shown in Table 1.

Table 1. Overall survival according to J-CAPRA risk score and age of patients in the J-CaP database (n = 15,727)

Age of patients (yr)	Year	J-CAPRA score		
		0–2	3–7	8+
All data	1	0.98	0.97	0.89
	3	0.93	0.85	0.6
	5	0.87	0.74	0.4
	7	0.81	0.64	0.27
≤65	1	0.99	0.98	0.91
	3	0.97	0.88	0.63
	5	0.95	0.76	0.43
	7	0.92	0.66	0.31
66–75	1	0.99	0.98	0.92
	3	0.95	0.89	0.62
	5	0.9	0.8	0.41
	7	0.85	0.71	0.25
>75	1	0.97	0.95	0.86
	3	0.91	0.8	0.55
	5	0.84	0.68	0.36
	7	0.77	0.56	0.28

J-CaP, Japan Study Group of Prostate Cancer.

4. Overall survival according to type of hormonal therapy in younger and older patients
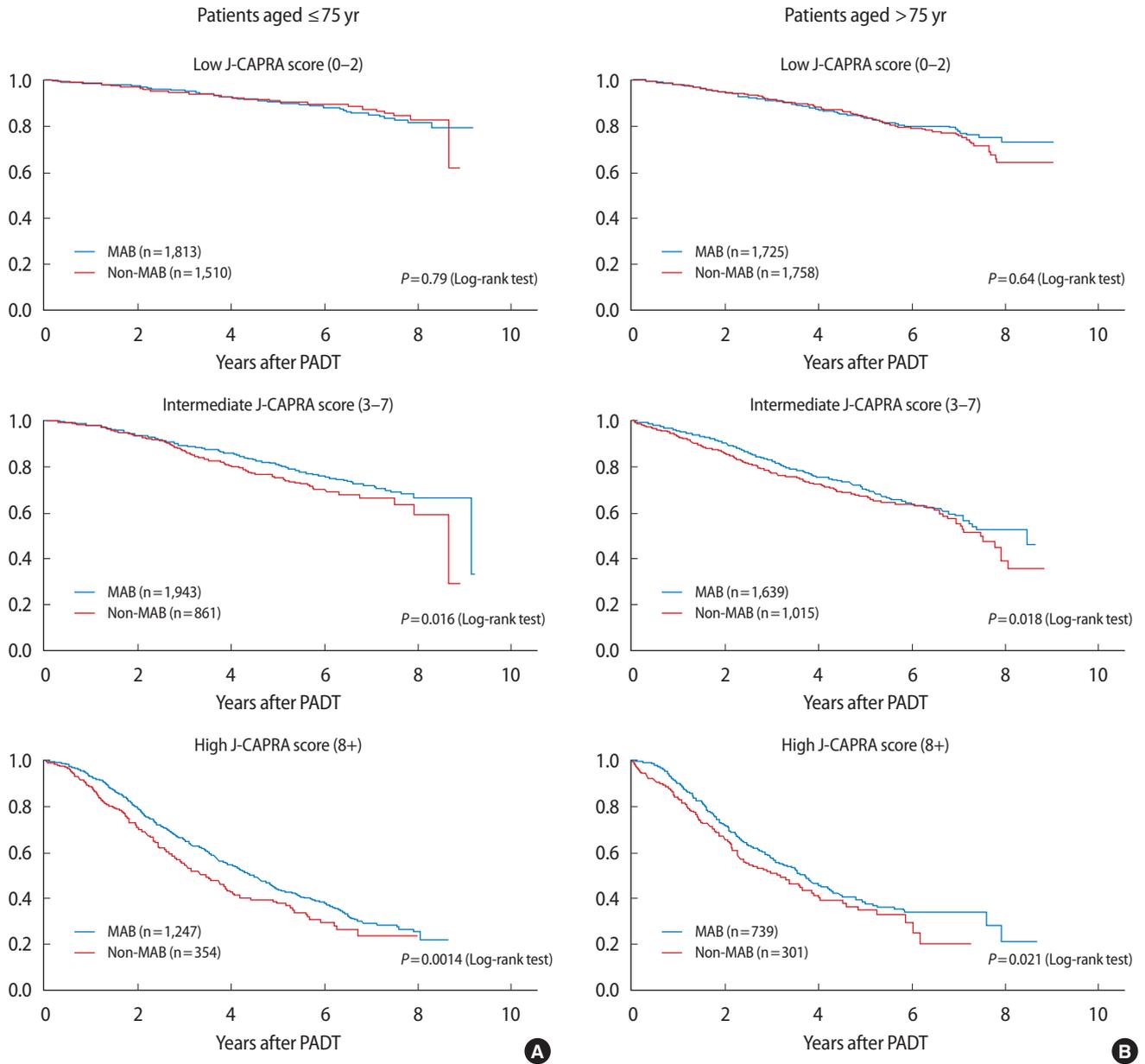
Overall survival according to J-CAPRA risk score for two age groups of patients (younger, ≤75 years; older, >75 years of age) who had received MAB or non-MAB hormonal therapy is shown in Fig. 3. In each age category the trend was similar with low-risk patients having a better overall survival than those with high-risk disease, regardless of type of hormonal therapy. In the younger patient subgroup (≤75 years), while there was no significant difference between MAB and non-MAB therapy in terms of overall survival for patients with low J-CAPRA risk scores, for those with intermediate and high risk scores there was a significant benefit observed in favour of MAB therapy: intermediate risk, $P = 0.016$; high risk, $P = 0.0014$. A similar pattern was observed for the older patient subgroup: for intermediate- and high-risk patients MAB therapy was associated with significantly better overall survival than non-MAB therapy ($P = 0.018$ and $P = 0.021$, respectively).

5. Occurrence of comorbidities

The occurrence of comorbidities at the time of diagnosis of prostate cancer and past history of disease is shown in Fig. 4. It was found that hypertension occurred in around 30% of patients and diabetes in just over 10%.

6. Multivariate analysis

A multivariate analysis of overall survival in younger (≤75 years) and older (>75 years) patients according to J-CAPRA score, MAB or non-MAB therapy, and three different comorbidities–hypertension, heart disease or stroke, diabetes, or other type of cancer–is shown in Table 2. The higher the J-CAPRA risk score, the greater the impact on overall survival. Low risk patients had significantly better overall survival than high-risk patients ($P < 0.0001$) regardless of age group. MAB therapy was associated with significantly improved overall survival compared with non-MAB therapy in both age groups (younger patient subgroup [hazard ratio, 0.81 vs. 1.00; $P < 0.001$], older patient subgroup [hazard ratio, 0.84 vs. 1.00; $P < 0.023$]). For the younger age subgroup, of the comorbidities analyzed, only diabetes and other type of cancer had a significant negative impact on overall survival ($P < 0.0001$). However, for the older age subgroup, all three comorbidity variables analyzed had a significant negative impact on overall survival (hypertension or heart disease or stroke, $P = 0.0027$; diabetes, $P = 0.019$; other cancer, $P < 0.0001$). In both age groups, MAB therapy was associated with around a 20% reduction in mortality compared with non-MAB therapy.

Fig. 3. Overall survival according to J-CAPRA risk score for patients aged ≤75 years (A) and patients aged >75 years (B) who received maximal androgen blockade (MAB) or non-MAB hormonal therapy. PADT, primary androgen deprivation therapy.
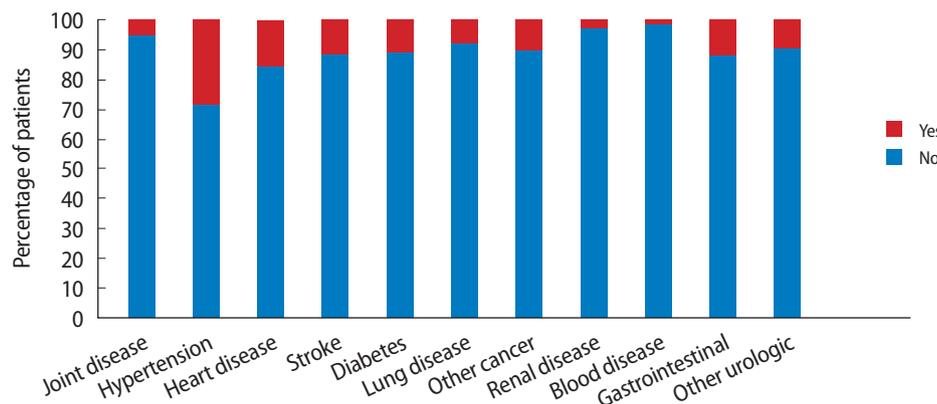
Fig. 4. Comorbidities and past history of disease at the time of diagnosis of prostate cancer.

Table 2. Multivariate analysis of factors that impact on overall survival in patients aged ≤75 years and patients aged >75 years

Factor & level	Patients aged ≤75 yr		Patients aged >75 yr	
	Hazard ratio	P-value	Hazard ratio	P-value
J-CAPRA score		<0.0001		<0.0001
0–2	1.00		1.00	
3–7	2.46		2.25	
8+	9.68		6.29	
Hormone therapy		0.0010		0.0023
Non-MAB	1.00		1.00	
MAB	0.81		0.84	
Comorbidity: hypertension or heart disease or stroke		0.2000		0.0027
No	1.00		1.00	
Yes	1.08		1.18	
Comobidity: diabetes		<0.0001		<0.019
No	1.00		1.00	
Yes	1.45		1.24	
Comobidity: other cancer		<0.0001		<0.0001
No	1.00		1.00	
Yes	1.90		1.40	

MAB, maximal androgen blockade.

DISCUSSION

Evidence from RCTs is now accumulating to suggest the greater benefits of MAB compared with non-MAB hormonal therapy, particularly in certain subgroups of patients [3-5]. The most recent of these studies reported a significant survival advantage for MAB compared with LHRH analog monotherapy in stage C and D1 patients but not stage D2 patients, and this was achieved without any reduction in tolerability [4]. These results suggest that CAB may be more effective in prostate cancer patients with early-stage disease, such as C or D1.

This analysis of registry data from the J-CaP database suggests that MAB for prostate cancer patients with intermediate- or high-risk disease has a significant benefit in terms of overall survival compared with LHRH analog monotherapy or surgical castration alone, and that better results may be achieved in older (≥75 years) patients.

Results from this analysis do need to be interpreted with caution as the data are not randomized which does make it difficult to draw firm conclusions and to compare with data from RCTs.

In the 1990s, while in theory MAB seemed like a useful hypothesis for prostate cancer therapy, the survival advantage compared with surgical or medical castration alone in published RCTs and meta-analyses was negligible and safety and tolerability data were lacking [11]. Results from this study and recent publications now suggest that the benefits of MAB in terms of survival may outweigh any risks, but this needs to be considered in the context of the individual patient's clinical characteristics and background [3-5].

In view of recent data on the benefits of MAB the American Society for Clinical Oncology recently revised its guidelines for the management of prostate cancer. Those published in 2004 noted that 'a small survival advantage' was likely with MAB over castration alone, but noted that the benefits should be balanced against great toxicity and reduced cost-effectiveness [12]. The 2006 update now recommends that MAB is considered as a therapeutic option for initial hormonal management of androgen-sensitive, metastatic, recurrent, or progressive disease [13].

The results of this current analysis also demonstrate that patient comorbidities are an important factor in determining overall survival, most notably in older patients and should be a key consideration when selecting appropriate therapy. Several recent studies have reported a relationship in patients with prostate cancer between ADT with LHRH therapy (with or without an antiandrogen) and an increased risk of cardiovascular disease; some studies, but not all, have also reported an increase in the risk of cardiovascular death [14-18]. This has focused discussion on the metabolic effects of ADT and the possible association with increased cardiovascular risk. As a result, advice for the prescribing clinician has been issued jointly by the American Heart Association, American Cancer Society, and American Urological Association which recommends monitoring blood pressure and lipid and blood glucose levels before the start of ADT, within 3–6 months after the start of therapy, and then on an annual basis if treatment is continued [19]. These recommendations apply to all forms

of ADT and there is no specific advice at the present time relating to MAB therapy.

The study undertaken by Akaza et al. [20] demonstrated no difference in overall survival between patients with localized prostate cancer treated with PADT and men of the same age in the general population, suggesting that there is no significant increase in mortality in men treated with PADT. These findings are supported by recent analyses showing that the incidence of cardiovascular events in patients registered in J-CaP database from 2001–2003 and treated with PADT was no greater than that expected in general Japanese population [8]. In addition, data from a large national prostate cancer patient registry in the USA, the Cancer of the Prostate Strategic Urologic Research Endeavor database, also demonstrated no increased risk of cardiovascular mortality with use of ADT [21].

Due to the particularly hormone-sensitive nature of the prostate cancer the search is continuing for new, more effective types of hormonal therapy and a range of different compounds is currently under investigation that act at various points along the pathway to androgen generation and target all possible sources: testicular, adrenal, those produced in the prostate gland itself or by other peripheral tissues. These include agents that exert their effects at the androgen receptor and those that inhibit hormone synthesis [22]. Such developments in therapy will undoubtedly be of particular importance for patients with metastatic prostate cancer which presents major therapeutic challenge once resistance to hormonal therapy develops. As clinicians are aware, when treating prostate cancer patients with PADT it is important to select an appropriate therapy for the individual patient that provides optimum efficacy while also minimizing adverse events. It is hoped that new, more selective antiandrogenic agents may also potentially reduce the incidence of the adverse events that are commonly associated with currently available hormonal therapy and mean that PADT could be used to treat a wider range of prostate cancer patients.

The overall results of this analysis of prostate cancer patients within the J-CaP database suggest that PADT in the form of a MAB regimen may provide significant survival benefits in some patients but that further data from RCTs and large registries are required to support the current thinking and to help identify patients who are most suited to this form of therapy.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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