$Lck_{486-494}$, $Lck_{488-497}$, $PSMA_{624-632}$, $EZH2_{735-743}$, and $PTHrP_{102-111}$. All peptides were prepared under Good Manufacturing Practice (GMP) compliance by American Peptide Company (San Diego, CA) and by PolyPeptide Laboratories (San Diego, CA), and were supplied in lyophilized vials; 4 mg, including inactive ingredients, under GMP compliance. Selected peptides were dissolved in 1 ml distilled water and emulsified with 1 ml of incomplete Freund's adjuvant (Montanide ISA-51VG; Seppic, Paris, France), under GMP compliance. Each of four peptides in 0.5 ml emulsion at a dose level of 1 mg/peptide (4 mg/2 ml), 1.5 ml emulsion at a dose level of 3 mg/peptide, and 2.5 mL emulsion at a dose level of 5 mg/peptide were injected subcutaneously into the thigh, the hip or the lower part of trunk area. Each peptide was independently injected nearby. EMP was administered orally as a 156.7 mg capsule, one capsule twice daily, for a total daily dose of 313.4 mg, half of the standard dose of EMP (626.8 mg/day) to avoid immunosuppression as reported in our previous study [19]. From the starting dose of 1 mg/peptide, subsequent dose levels were increased after the evaluation of the safety data by the Data and Safety Monitoring Committee (DSMC) according to the dose escalation design of the protocol. The initial cohort included six patients. If the DSMC recommended proceeding to the next level as a result of the safety evaluation of the prior level, new six patients were enrolled. The highest dose level enrolled three patients at first and was evaluated the safety data by the DSMC to include additional three patients. The maximum acceptable dose (MAD) was defined as the lowest dose level at which at least two-thirds of patients experienced grade 2 or greater injection site reactions after the sixth treatment. The maximum tolerated dose (MTD) was defined as the lowest dose level at which more than one-third of patients experienced grade 3 or greater systemic adverse events caused by ITK-1 after the sixth treatment. Adverse events were graded according to the CTCAE version 3.0 and were coded using MedDRA/J (Medical Dictionary for Regulatory Activities Terminology/Japanese) version 12.0. Patients who experienced no significant (≥CTCAE grade3) adverse events and no disease progression, and signed informed consent were eligible to extend treatment until disease progression or unacceptable adverse events occurred, or the patient met other withdrawal criteria.

Pretreatment and Follow-Up Studies

A complete history, physical examination, and routine laboratory studies, including complete blood counts, biochemical tests, ECG, relevant radiologic studies, PSA, and urinalysis were performed before treatment and repeated after every six injections.

Immune Responses

For evaluation of immune responses, peptide-specific CTL precursors in PBMCs and peptide-specific IgG levels in plasma were measured as described previously [13]. Also, peptide-specific IgG levels were measured using patient's plasma of the screening examination to select the best peptides. Briefly, 30 ml of peripheral blood samples were obtained from each patient to measure peptide specific CTL and IgG prior to vaccination, at the fourth and after the sixth vaccinations, and after every sixth vaccination in the extension study, and then the PBMCs and plasma were isolated by Ficoll–Conray density gradient centrifugation. We reported that the IgG specific to each peptide measured by Luminex system as the fluorescence intensity unit (FIU) could frequently be detected in pre- and post-vaccination plasma, and the level of peptide-specific IgG is a laboratory marker that predicts clinical responses to the PPV with a good relationship to overall survival [13,20]. Therefore, peptides were chosen on the basis of evaluation of peptide-specific IgG levels in plasma. Peptide-specific CTL precursors in PBMCs were detected using a previously reported culture method [21]. Briefly, PBMCs (1×10^5 cells/well) were incubated with 10 μM of each peptide in U-bottom-type 96-well microculture plates (Nunc, Roskilde, Denmark) in 200 μl of culture medium. The culture medium consisted of 45% RPMI-1640 medium, 45% AIM-V® medium (Invitrogen Corp., Carlsbad, CA), 10% FCS, 20 U/ml of interleukin-2 (IL-2), and 0.1 mM MEM nonessential amino acid solution (Invitrogen Corp.), 36 mg/L gentamicin sulfate (Wako Pure Chemical Industries, Ltd., Osaka, Japan). Half of the medium was removed and replaced with new medium containing a corresponding peptide (20 μM) every 3 days for up to 12 days. On the 12th day of the culture, 24 hr after the last stimulation, these cells were harvested, washed three times, and then tested for their ability to produce IFN-γ in response to C1R-A2402 cells preloaded with either a corresponding peptide or HIV peptide (RYLRQQLLGI) as a negative control in HLA-A24. The target cells (C1R-A2402, 1×10^4/well) were pulsed with each peptide (10 μM) for 2 hr, and then effector cells (1×10^5/well) were added to each well with a final volume of 200 μl. After incubation for 18 hr, the supernatants (100 μl) were collected, and the amounts of IFN-γ were measured using an ELISA (limit of sensitivity: 10 pg/ml). All experiments were performed in quadruplicate assay.

Definition of Treatment Outcomes

Outcomes were assessed by post-therapy changes in serum PSA and immune responses. A post-therapy

TABLE I. Baseline Demographics

Characteristics	No. of patients (%)
No. of patients	15
Age, years	
Median	73
Range	63–78
ECOG PS	
0	14 (93)
1	1 (7)
Gleason score	
7	3 (20)
8	5 (33)
9	4 (27)
10	1 (7)
Unknown	2 (13)
PSA (ng/mL)	
Median	39.6
Range	0.2–354.4
Site(s) of metastasis	
None	4 (27)
Lymph node	2 (13)
Bone	6 (40)
Lymph node + bone	1 (7)
Other	2 (13)
Local therapy	
Prostatectomy	4 (27)
EBRT	3 (20)
No definitive local therapy	8 (53)
Hormone therapy	
Primary therapy only	1 (7)
≥2 therapies	14 (93)
Chemotherapy	
EMP	15 (100)
Other	2 (13)

ECOG PS, Eastern Cooperative Oncology Group performance status; PSA, prostate-specific antigen; EBRT, external-beam radiation therapy; EMP, estramustine phosphate.

decrease of PSA to a normal range was defined as a complete response (CR) and a decrease in PSA of ≥50% from baseline was defined as a partial response (PR) in the phase I study. Also, a post-therapy PSA decrease of <50% or an increase >25% from baseline were interpreted as no change (NC) [22] and PSA above 125% of the baseline PSA value was defined as PD. Positive immune responses were defined as post-IgG levels/pre-IgG levels ≥3, post-IFN-γ levels/pre- IFN-γ levels ≥3, respectively. All patients were followed up every 3 months for life. Data, except the survival data, were analyzed by November 2009 using SAS (Statistical Analysis System) software version 9.1.3. The Student's *t*-test and the chi-square test were used to compare quantitative and categorical variables, respectively. Overall survival was calculated from the study registration date to the date of the last follow-up or the death from any cause. The Kaplan–Meier method was used to estimate product-limit estimate curves with the survival data obtained in March 2010. Tests results were considered significant at a two-sided significance level of 5%. The analysis was performed by intent to treat.

RESULTS

Patient Characteristics

Fifteen patients were recruited to the study between April 2006 and September 2007. Patient characteristics are listed in Table I. All patients were HLA-A24-positive, and had hormone and EMP refractory prostate cancer. In addition, all 15 patients were evaluated for the safety and the efficacy of the PPV treatment.

Dose Escalation

The dose-escalation scheme is presented in Table II. Maximum dose escalation preplanned for each peptide of 5 mg/2.5 mL (4 peptides, 20 mg/10 mL) was achieved. There were no treatment-related grade 3 or 4 adverse events or deaths in this study. Grade 2 injection site reactions were observed in two of six patients in the first dose level of 1 mg/peptide, and five of six patients in the second dose level of 3 mg/peptide after the sixth treatment. At the 5 mg/peptide dose

TABLE II. The Results of Dose-Escalation in Phase I Study

	No. of patients		No. of patients	
Peptides dose level (mg/peptide)	Enroll	Discontinued or skipped[a]	MAD (≥grade 2 injection site reaction)	MTD (≥grade 3 systemic treatment-related AE)
1	6	0/6	2/6	0/6
3	6	0/6	5/6	0/6
5	3	3/3	3/3	0/3
Total	15	3/15	10/15	0/15

MAD, maximum acceptable dose; MTD, maximum tolerated dose; AE, adverse event.
[a]Patients were discontinued or skipped the treatment because both widespread grade 2 injection site reactions and patients' own requests.

level, three patients were treated, but the vaccination was skipped or discontinued in all three patients considering the ethical viewpoint because of patients' own requests and physical burden, caused by widespread grade 2 injection site reactions. After these treatment-related adverse events, two of three 5 mg/peptide dose level patients were entered in the extension study and then the dose level was reduced to 3 mg/peptide during treatment. The DSMC reviewed the results and recommended stopping the additional three enrollments for the dose level of 5 mg/peptide. Subsequently, the MAD for PPV was calculated to be 8.643 mg/4 peptide (2.161 mg/peptide) based on the logistic regression model.

Adverse Events

There were no treatment-related serious adverse events and no grade 3 or greater adverse events in the phase I study. In contrast, a grade 3 injection site reaction and a grade 3 pyrexia occurred in one patient each during the extension study. All treatment-related adverse events observed in whole study (phase I and extension study) are listed in Table III. The primary nonhematologic treatment-related adverse events were injection site reaction (93.3%), malaise (33.3%), edema peripheral (33.3%), and fatigue (20.0%). These adverse events were manageable with routine intervention. Hematologic adverse events were, grade 1 white blood cell count increased and grade 1–2 lymphocyte count decreased occurred in 4 of 15 (26.7%) and 3 of 15 (20.0%) patients, respectively. One patient at a dose level of 5 mg/peptide had a grade 1 blood fibrinogen increased, and another patient at a dose level of 3 mg/peptide had grade 1 blood triglycerides increased during the first course, and these changes returned to normal levels on the next course.

Immune Response

The best peptides for each patient were selected based on peptide-specific IgG levels for each peptide at the screening examination (data not shown). The results of the immune response in the first course are given in Table IV. After the sixth vaccination, IgG responses were increased in one of six patients with 1 mg/peptide, four of six patients with 3 mg/peptide, and two of three patients with 5 mg/peptide tested. CTL responses measured by IFN-γ release assay were increased in four of six patients with 1 mg/peptide, six of six patients with 3 mg/peptide, and zero of three patients with 5 mg/peptide tested.

Clinical Response

PSA response after the sixth vaccination was CR in one patient (6.7%) receiving 3 mg/peptide, PR in one patient (6.7%) receiving 1 mg/peptide, and PD in two patients (13.3%) receiving 5 mg/peptide. At the time of data analysis, nine patients had died and all deaths were attributed to prostate cancer or metastases. The median follow-up time for all patients was 23.8 months, ranging from 3.0 to 38.3 months. None of the patients was lost to follow-up during this analysis. The median overall survival was 23.8 months for all 15 patients (95% CI, lower limit was 15.6 months, upper limit was not estimated; Fig. 1).

DISCUSSION

We performed a multicenter, open-label, phase I trial to evaluate the safety, tolerability, immune response, and PSA response of a combination of escalating doses of PPV and low-dose EMP. All patients had hormone and EMP-refractory prostate cancer. The treatment regime was well tolerated at all dose levels, except the injection site reaction at the highest dose level of 5 mg/peptide observed in all three patients enrolled, and no MTD was established in this trial. The most common adverse event was injection site reaction. The concept of dose escalation in a phase I trial to identify an MTD may not be applicable to most therapeutic cancer vaccines [23]. Peptide vaccines based on non-mutated melanoma antigens such as MART-1/Melan A and gp100 were initially evaluated in a phase I setting, at doses ranging from 0.1 to 10 mg [24,25]. However, no toxicity was observed even at the highest doses, and in vitro analysis did not reveal any correlation between the peptide dose and the generation of specific T-cell reactivity from the PBMCs of the vaccinated patients. Neither the safety nor efficacy of the vaccine can be assessed in patients with a blunted immune response since both safety and efficacy depend on the immune response. In contrast, our initial trial for colorectal cancer patients with 0.3, 1, and 3 mg/injections of SART3 peptide showed that a dose of 3 mg/injection was better than that of 0.3 and 1 mg/injection based on the induction of cellular immune responses to both tumor cells and peptides [26]. The current phase I study also showed that a dose of 3 mg/injection was better than those of 1 and 5 mg/injection based on the induction of cellular immune responses to peptides, although total doses of four peptides were 4 mg/2 mL, 12 mg/6 mL, and 20 mg/10 mL. Under these conditions, there were no serious adverse events caused by ITK-1; however, grade 2 injection site reactions were observed in two of six patients receiving 1 mg/0.5 mL/peptide, five of six patients receiving 3 mg/1.5 mL/peptide, and three of three patients receiving 5 mg/2.5 mL/peptide in the phase I study. The vaccination was skipped or discontinued in three of three patients receiving 5 mg/2.5 mL/peptide

TABLE III. Treatment-Related Adverse Events for Castration-Resistant Prostate Cancer

	No. of patients experienced treatment-related adverse events during phase I study/whole study[a] by grade									Total (15 patients)	
	1 mg/peptide group (6 patients)			3 mg/peptide group (6 patients)			5 mg/peptide group (3 patients)			All grade	
MedDRA/J ver12.0 symptom: preferred Trem(PT)	G1 (PI/ Whole)	G2 (PI/ Whole)	G3 (PI/ Whole)	G1 (PI/ Whole)	G2 (PI/ Whole)	G3 (PI/ Whole)	G1 (PI/ Whole)	G2 (PI/ Whole)	G3 (PI/ Whole)	P I	Whole
Vomiting	1/1									1 (6.7%)	1 (6.7%)
Ventricular extrasystoles	0/1										1 (6.7%)
Fatigue	0/1	0/1		1/0	0/1					1 (6.7%)	3 (20.0%)
Injection site reaction	2/2	2/3		1/1	5/4	0/1		3/3		13 (86.7%)	14 (93.3%)
Malaise	1/2			0/1	0/1		0/1			1 (6.7%)	5 (33.3%)
Oedema peripheral	1/2	0/1			0/1		0/1			1 (6.7%)	5 (33.3%)
Pyrexia						0/1					1 (6.7%)
Aspartate aminotransferase increased	0/1										1 (6.7%)
Blood fibrinogen increased							1/1			1 (6.7%)	1 (6.7%)
Blood triglycerides increased				1/1						1 (6.7%)	1 (6.7%)
Crystal urine present	0/1										1 (6.7%)
Blood urine present				0/1							1 (6.7%)
Lymphocyte count decreased	1/1	1/1			1/1					3 (20.0%)	3 (20.0%)
Neutrophil count increased	0/1										1 (6.7%)
Urinary casts	0/1										1 (6.7%)
White blood cell count increased	0/1			1/2			1/1			2 (13.3%)	4 (26.7%)
White blood cells urine positive	0/1			0/1							2 (13.3%)
Bacteria urine identified				0/1							1 (6.7%)
Dizziness				0/1							1 (6.7%)
Dizziness postural				0/1							1 (6.7%)
Headache				1/0	0/1					1 (6.7%)	1 (6.7%)
Insomnia		0/1									1 (6.7%)
Cough	0/1										1 (6.7%)
Rash generalized					0/1						1 (6.7%)

[a]Whole study means phase I and extension study.

TABLE IV. Immunorogical Responses During the Personalized Peptide Vaccination

Dose of peptide	Pts No.	Peptide	Anti-peptide IgG response (FIU)[a]				Anti-peptide cellular response (pg/ml)[b]			
			Pre	Post (fourth)	Post (after sixth)	Increased response (after sixth)	Pre	Post (fourth)	Post (after sixth)	Increased response (after sixth)
1 mg	1	Lck-486	94	90	81	—	ND	ND	ND	—
		PSMA-624	<5	<5	<5	—	ND	ND	ND	—
		PTHrP-102	42	30	23	—	113	ND	ND	—
		SART3-109	31	24	21	—	ND	ND	ND	—
	2	Lck-486	310	206	976	Positive	667	ND	204	—
		MRP3-1293	38	21	28	—	ND	ND	186	Positive
		SART2-93	20	11	9	—	ND	ND	656	Positive
		SART3-109	27	13	18	—	899	ND	ND	—
	3	Lck-486	102	102	114	—	ND	78	ND	—
		Lck-488	45	46	52	—	462	ND	ND	—
		MRP3-1293	52	45	50	—	ND	ND	ND	—
		PAP-213	252	210	215	—	ND	ND	ND	—
	4	Lck-486	200	199	247	—	ND	ND	1,393	Positive
		Lck-488	<5	<5	<5	—	ND	ND	472	Positive
		PSA-248	117	99	109	—	ND	ND	ND	—
		PTHrP-102	171	138	142	—	564	ND	ND	—
	5	Lck-486	575	364	396	—	ND	117	57	—
		Lck-488	144	102	92	—	ND	ND	439	Positive
		MRP3-1293	91	64	51	—	133	160	ND	—
		PAP-213	90	70	77	—	3,764	ND	114	—
	6	MRP3-1293	779	586	411	—	ND	477	ND	—
		PSA-248	804	756	1,825	—	ND	ND	ND	—
		PTHrP-102	502	414	310	—	ND	93	753	Positive
		SART3-109	142	152	83	—	ND	ND	3,276	Positive
3 mg	7	Lck-486	202	216	9,028	Positive	ND	1,636	ND	—
		MRP3-1293	29	21	22	—	ND	ND	ND	—
		PAP-213	<5	<5	5	—	274	ND	1,494	Positive
		PSA-248	11	12	1,902	Positive	173	ND	ND	—
	8	Lck-486	298	261	287	—	2,543	ND	ND	—
		Lck-488	10	9	11	—	ND	ND	598	Positive
		MRP3-1293	23	21	23	—	ND	ND	ND	—
		PAP-213	8	5	9	—	ND	ND	2,613	Positive
	9	Lck-486	329	290	308	—	ND	ND	72	—
		Lck-488	128	103	106	—	ND	119	627	Positive
		MRP3-1293	53	36	40	—	ND	1,706	ND	—
		PAP-213	<5	<5	10,992	Positive	ND	683	ND	—

(Continued)

TABLE IV. (*Continued*)

Dose of peptide	Pts No.	Peptide	Anti-peptide IgG response (FIU)[a] Pre	Post (fourth)	Post (after sixth)	Increased response (after sixth)	Anti-peptide cellular response (pg/ml)[b] Pre	Post (fourth)	Post (after sixth)	Increased response (after sixth)
	10	Lck-486	826	1,632	16,376	Positive	127	ND	7,014	Positive
		Lck-488	21	22	48	—	117	227	115	—
		MRP3-1,293	21	22	24	—	ND	109	ND	—
		PAP-213	15	15	60	Positive	189	ND	285	—
	11	Lck-208	19	18	21	—	211	54	ND	—
		Lck-486	434	349	105	—	ND	ND	ND	—
		Lck-488	12	12	12	—	ND	ND	5,258	Positive
		PTHrP-102	102	99	135	—	ND	2,991	2,934	Positive
	12	Lck-486	392	549	348	—	ND	ND	1,136	Positive
		Lck-488	87	96	64	—	ND	ND	ND	—
		PSA-248	157	2,653	18,163	Positive	ND	ND	ND	—
		SART3-109	76	87	58	—	ND	ND	794	Positive
5 mg	13	Lck-486	183	231	861	Positive	184	103	104	—
		PAP-213	39	35	8,490	Positive	232	ND	ND	—
		SART2-93	56	49	51	—	59	215	ND	—
		SART3-109	31	31	38	—	391	ND	165	—
	14	Lck-486	162	120	2,950	Positive	185	348	126	—
		MRP3-1293	29	27	149	Positive	97	104	ND	—
		SART2-161	16	17	27	—	178	200	263	—
		SART3-109	23	20	108	Positive	1,285	117	1,024	—
	15	Lck-486	809	837	916	—	1,339	ND	ND	—
		MRP3-1293	710	543	550	—	251	ND	ND	—
		SART2-161	72	46	57	—	ND	ND	55	—
		SART3-109	311	248	236	—	100	ND	110	—

[a]Values indicate fluorescence intensity unit (FIU) of IgG antibodies reactive to each peptide.
[b]Values indicate the mean of specific interferon-γ production in positive wells reactive to each peptide.

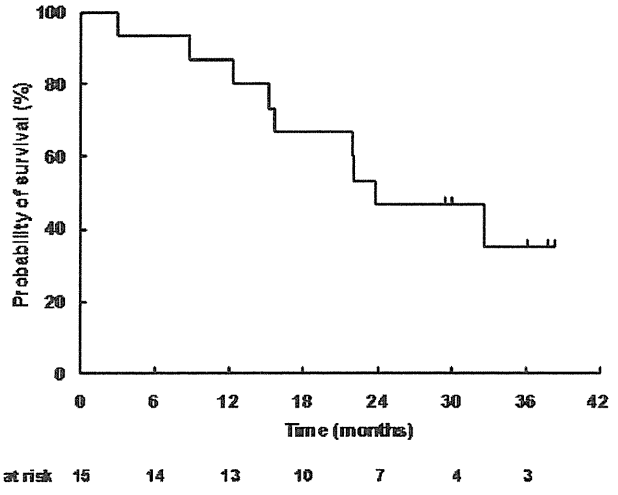

Fig. 1. Kaplan–Meier estimates of overall survival for 15 patients treated by personalized peptide vaccination with low-dose estramustine. Median overall survival is 23.8 months.

because of both widespread grade 2 skin reactions and patients' own requests. Subsequently, we calculated MAD as 8.643 mg/4 peptides in this study. Therefore, considering the adverse events, tolerability, and immune responses, the 3 mg/1.5 mL/peptide dose of PPV will be recommended for further clinical trials.

In the present study, CTL responses measured by IFN-γ release assay and IgG responses were enhanced in 10/15 (66.7%) and 7/15 (46.7%) of the examined patients, respectively, and in the PSA response, CR and PR was one patient each (6.7%) and PD was two patients (13.3%) after the sixth vaccination. In addition, the long-term (23.8 months) median survival time after combination therapy with PPV and low-dose EMP observed in the extension study indicated that this treatment suppresses tumor growth. However, the exact mechanism of this interaction is unclear and further studies are needed.

In conclusion, the results of safety, immune responses, and improved overall survival without MTD, as well as the consistency between these results and the data from our previous trials [4,19,27], could lead to us to the next phase of randomized clinical trial wherein we can confirm the survival benefit of such personalized immunotherapy in HLA-A24 positive patients with CRPC.

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Gleason Score Correlation Between Biopsy and Prostatectomy Specimens and Prediction of High-grade Gleason Patterns: Significance of Central Pathologic Review

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OBJECTIVES To investigate the significance of dedicated central pathologic review for Gleason score (GS) correlation between the biopsy and radical prostatectomy (RP) specimens and the prediction of high-grade Gleason patterns. A discrepancy in the GS between the biopsy and RP specimens has been reported.

METHODS The Clinicopathological Research Group for Localized Prostate Cancer disease registry collated the data from 1629 patients who had undergone RP from 1997 to 2005. All biopsy and RP specimens were retrospectively re-evaluated by 2 central uropathologists according to the International Society of Urological Pathology consensus. The GS correlation between the biopsy and RP specimens and the presence of high-grade Gleason patterns (4 or 5) were recorded. The GS was categorized into 5 groups (2-4, 5-6, 3 + 4, 4 + 3, and 8-10).

RESULTS Central review significantly increased the exact concordance rate and decreased the undergrading and overgrading rates between the biopsy and RP specimens compared with local review ($P < .05$ for all). In each GS or prostate-specific antigen group, the central review biopsy GS had a significantly greater exact concordance rate with the RP specimen GS compared with the local review biopsy GS ($P < .05$ for all). Regarding high-grade Gleason patterns in the RP specimens, central review showed significantly greater sensitivity, positive predictive value, and negative predictive value than local review ($P < .05$ for all).

CONCLUSIONS We have demonstrated that central review using the International Society of Urological Pathology consensus improves the GS correlation and better predicts high-grade Gleason patterns compared with local review. We recommend central pathologic review by dedicated uropathologists for multi-institutional studies using data from prostate biopsy and RP specimens. UROLOGY 77: 407–411, 2011. © 2011 Elsevier Inc.

The Gleason grading system, proposed by Gleason[1] and represented as the Gleason score (GS) for each case, is the most widely used histologic grading system for prostate cancer. The GS in both biopsy and radical prostatectomy (RP) specimens is a powerful prognostic factor.[2,3] Accurate GS correlation between the biopsy and RP specimens is mandatory for preoperative estimation of the disease and for the planning treatment of each patient. However, the biopsy GS has been reported to have been undergraded in 18%-60% and overgraded in 6%-25% of specimens compared with the RP specimen GS.[4-11] Investigator error is one important factor for the discrepancy; thus, pathologic assessment by dedicated uropathologists might improve the GS correlation between the biopsy and RP specimens. Modern GS assessment according to the 2005 International Society of Urological Pathology (ISUP) consensus, reflecting contemporary changes regarding prostate cancer and the Gleason grading system, has shown better GS correlation than the previous assessment.[12] Pathologic assessment by dedicated uropathologists in a single academic institution has also shown better GS correlation than outside assessment.[6,11] However, the usefulness of pathologic assessment by dedicated uropathologists using the ISUP consensus for a large RP series from multiple institutions has not yet been studied.

Although high-grade Gleason patterns (4 or 5) in RP specimens, either a primary/secondary pattern or a ter-

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tiary pattern, have been reported to be related to a poor outcome, it remains unclear how effectively the biopsy GS determined by pathologic assessment by dedicated uropathologists will predict for high-grade Gleason patterns in the RP specimens.[13-15]

In the present, large-scale, multicenter study, we used the pathologic assessment by dedicated uropathologists according to the ISUP consensus for the biopsy and RP specimens from a large RP series with high-grade biopsy GSs using data from the Clinicopathological Research for Localized Prostate Cancer (CRPC) disease registry. The CRPC collates data from patients with clinically localized prostate cancer accrued from 108 academic and community practices throughout Japan. From 1997 to 2005, approximately 5000 patients with clinically localized prostate cancer who had undergone RP were consecutively enrolled into the CRPC registry after obtaining institutional review board approval from each institution.

MATERIAL AND METHODS

Patient Population

According to the CRPC data, the pathologic slides of the biopsy and RP specimens were available for 1650 patients with Stage cT1c-T3 disease and no preoperative therapy at 48 institutions that agreed to send the pathologic slides for central review. After excluding 21 patients (1.3%) without cancer cells in the biopsy specimens by central review, 1629 patients constituted the final cohort for the present study. In all patients, the diagnosis was made by systemic biopsy (≥6 cores). A total of 365 patients (22.4%) had only 6 cores taken at biopsy; 760 patients (46.7%) had ≥10 cores on taken at biopsy. The median number of biopsy cores taken was 8 (range 6-33). All RP specimens were processed using the whole mount technique at each institution. Preoperative information, including the serum prostate-specific antigen levels, and the original pathologic reports were available for all patients. The clinical stage was determined from the digital rectal examination findings and assigned according to the 2002 American Joint Committee on Cancer staging system.

Pathologic Analysis

The biopsy GS of each patient's original pathologic report was recorded as the local review biopsy GS. All pathologic slides and the biopsy and RP specimens were sent to, and reviewed by, 2 dedicated uropathologists (K.K. and T.S.) who were unaware of the original pathologic reports of each patient. In addition, the 2 uropathologists were unaware of the results from the biopsy specimens of each patient when reviewing the matching RP specimens, because the review of the RP specimens was separated from the review of the biopsy specimens. The Gleason pattern was assigned as the central review biopsy and RP GS according to the modified Gleason grading system using the ISUP consensus.[16] The GS was categorized into 5 groups (2-4, 5-6, 3 + 4, 4 + 3, and 8-10). For the biopsy specimens with multiple positive cores, a global GS was recorded, because the GS of each core was not available in most (>95%) of the original pathologic reports. For central review, the reporting rules for a secondary pattern occupying <5% and a tertiary pattern conformed to the ISUP consensus.[16] For the RP specimens, the global GS considering the entire tumor within the prostate as 1 lesion was recorded. A tertiary Gleason pattern in the RP specimens was not reflected as a primary or secondary pattern on the final RP GS. The presence of high-grade Gleason patterns (4 or 5), including tertiary patterns, in the RP specimens was recorded.

Statistical Analysis

Spearman's rank correlation coefficients for the GS in the biopsy and RP specimens were generated. The chi-square test was used for the comparison of the exact GS concordance rate between the local and central pathologic review and for the sensitivity, specificity, positive predictive value, and negative predictive value for the depiction of high-grade Gleason patterns. Two-sided P values were calculated; the significance level was set at 5%. All statistical analyses were performed using the Statistical Package for Social Sciences, version 17.0 (SPSS, Chicago, IL).

RESULTS

Clinical Characteristics

For the 1629 patients whose CRPC data were analyzed, the median age was 65 years (range 44-84), and the median prostate-specific antigen level 8.0 ng/mL (range 0.5-85.9). Of the 1629, patients, 1058 (64.9%) had Stage cT1c disease.

GS in Biopsy and RP Specimens

By central review, no patient (0%) had GS 2-4 disease in the biopsy specimens compared with 107 patients (6.6%) who had GS 2-4 by local review. Of the 107 patients with local review biopsy GS of 2-4, central review found a biopsy GS of 5-6, 3 + 4, 4 + 3, and 8-10 in 66 (61.7%), 35 (32.7%), 4 (3.7%), and 2 (1.9%), respectively. In the other GS groups, the distribution of the central biopsy GS was 5-6 in 545 (33.5%), 3 + 4 in 602 (37.0%), 4 + 3 in 257 (15.8%), and 8-10 in 225 (13.8%). The corresponding distribution by local review for the biopsy GS was 687 (42.2%), 379 (23.3%), 192 (11.8%), and 264 (16.2%; Table 1). Of the patients with a biopsy GS of 5-6, 3 (0.6%) of 545 by central review and 138 (20.1%) of 602 by local review had GS 5. Exact concordance between the local and central biopsy GS was observed for 841 patients (51.6%). The undergrading and overgrading rate for local review was 32.6% and 15.8%, respectively. Spearman's rank correlation coefficient for local biopsy GS and central biopsy GS was 0.607. The central review RP GS distribution for GS 5-6, 3 + 4, 4 + 3, and 8-10 was 423 (26.0%), 675 (41.4%), 363 (22.3%), and 168 (10.3%), respectively.

GS Correlation Between Biopsy and RP Specimens

Table 2 lists the correlation between the local review biopsy GS and central review RP GS. The exact concordance rate and the concordance rate within ±1 GS group was 41.3% (672 of 1629) and 81.7% (1331 of 1629), respectively. The undergrading and overgrading rate for

Table 1. Biopsy Gleason score correlation between local review and central review

Local Review Biopsy GS	Central Review Biopsy GS (n)					Exact Concordance Rate (%)	Local Review	
	2-4	5-6	3 + 4	4 + 3	8-10		Undergrading Rate (%)	Overgrading Rate (%)
2-4 (n = 107)	0	66	35	4	2	0.0	100.0	0.0
5-6 (n = 687)	0	388	233	50	16	56.5	43.5	0.0
3 + 4 (n = 379)	0	64	225	62	28	59.4	23.7	16.9
4 + 3 (n = 192)	0	13	60	84	35	43.8	18.2	38.0
8-10 (n = 264)	0	14	49	57	144	54.5	0	45.5
Total (n = 1629)	0	545	602	257	225	51.6	32.6	15.8

GS, Gleason score.

Table 2. Gleason score correlation between local review biopsy and central review prostatectomy specimens

Local Review Biopsy GS	Central Review RP GS (n)					Exact Concordance Rate (%)	Undergrading Rate in Biopsy (%)	Overgrading Rate in Biopsy (%)
	2-4	5-6	3 + 4	4 + 3	8-10			
2-4 (n = 107)	0	42	48	14	3	0.0	100.0	0.0
5-6 (n = 687)	0	282	286	97	22	41.0	59.0	0.0
3 + 4 (n = 379)	0	73	204	86	16	53.8	26.9	19.3
4 + 3 (n = 192)	0	16	65	85	26	44.3	13.5	42.2
8-10 (n = 264)	0	10	72	81	101	38.3	0.0	61.7
Total (n = 1629)	0	423	675	363	168	41.3	39.3	19.5

RP, radical prostatectomy; GS, Gleason score.

Table 3. Gleason score correlation between central review biopsy and prostatectomy specimens

Central Review Biopsy GS	Central Review RP GS (n)					Exact Concordance Rate (%)	Undergrading Rate in Biopsy (%)	Overgrading Rate in Biopsy (%)
	2-4	5-6	3 + 4	4 + 3	8-10			
2-4 (n = 107)	0	0	0	0	0	—	—	—
5-6 (n = 687)	0	335	173	27	10	61.5	38.5	0.0
3 + 4 (n = 379)	0	83	391	113	15	65.0	21.3	13.8
4 + 3 (n = 192)	0	2	76	160	19	62.3	7.4	30.4
8-10 (n = 264)	0	3	35	63	124	55.1	0.0	44.9
Total (n = 1629)	0	423	675	363	168	62.0	21.9	16.1

Abbreviations as in Table 2.

the biopsy specimens was 39.3% and 19.5%, respectively. Of the 107 patients with a biopsy GS of 2-4, all had an RP GS of ≥5-6, including 65 patients (60.1%) with a RP GS of ≥7. Spearman's rank correlation coefficient for the local biopsy GS and central RP GS was 0.459.

Table 3 lists the correlation between the central biopsy GS and the central RP GS. The exact concordance rate and the concordance rate within ±1 GS group was 62.0% (1010 of 1629) and 94.4% (1537 of 1629), respectively. The undergrading and overgrading rate for the biopsy specimens was 21.9% and 16.1%, respectively. Central review had a significantly greater exact concordance and lower undergrading and overgrading rates than did the local review ($P < .05$ for all). Spearman's rank correlation coefficient for central biopsy GS and central RP GS was 0.687. In each GS group, the central review biopsy GS (GS 5-6, 61.5%; 3 + 4, 65.0%; 4 + 3, 62.3%; and 8-10, 65.1%) had a significantly greater exact concordance rate than did the local review biopsy GS (GS 5-6, 41.0%; 3 + 4, 53.8%; 4 + 3, 44.3%; and 8-10, 38.3%; $P < .05$ for all). In each prostate-specific antigen group, the central review biopsy GS (<4.0 ng/mL, 56.6%; 4.1-10 ng/mL, 64.1%; 10.1-20 ng/mL, 60.7%; and >20 ng/mL, 56.4%) had a significantly greater exact concordance rate than the local review biopsy GS (<4.0 ng/mL, 56.6%; 4.1-10 ng/mL, 64.1%; 10.1-20 ng/mL, 60.7%; and >20 ng/mL, 56.4%; $P < .05$ for all).

High-Grade Gleason Patterns (4 or 5)

The number of patients with Gleason pattern 4 or 5 in the biopsy GS as a primary or secondary pattern was 846 (51.9%) in the local review and 1084 (66.6%) in the central review.

Overall, 1371 patients (84.2%) had Gleason pattern 4 or 5 on RP specimens on the central pathology review of the RP specimens. Of these, 1206 (88.0%) had Gleason pattern 4 or 5 as the primary or secondary pattern. The remaining 165 (12.0%) with RP GS 3 + 3 had a high-grade Gleason pattern of <5% on the RP specimens.

Table 4 lists the correlation of high-grade Gleason patterns between the biopsy GS and RP specimens. The central review GS had significantly greater sensitivity and a significantly greater positive and negative predictive values ($P < .05$ for all).

Table 4. High-grade Gleason patterns (4 or 5) in biopsy Gleason score and prostatectomy specimens

Review	High-Grade GP in Biopsy GS	High-Grade GP in RP Specimens (n)		Sensitivity	Specificity	PPV	NPV
		Positive	Negative				
Local	Positive	797	49	0.581	0.810	0.942	0.140
	Negative	574	206				
Central	Positive	1052	32	0.767	0.876	0.970	0.415
	Negative	319	226				
P value				<.001	.053	.003	<.001

GP, Gleason pattern; NPV, negative predictive value; PPV, positive predictive value; other abbreviations as in Table 2.

COMMENT

In the pretreatment setting for prostate cancer in which clinicians can only use the biopsy information for histologic grade, a more accurate GS correlation between the biopsy and RP specimens must result in more precise evaluation of the disease, regardless of the treatment type planned. However, studies investigating the GS correlation between the biopsy and RP specimens have shown considerable discrepancy—especially of undergrading in biopsy specimens.[4-11] Although the number of patients involved in these studies has varied from 28 to 1455, very few men had high-grade biopsy GSs.[8-10] The present study included the largest number of patients with high-grade biopsy GS (local review 264, central review 168) for investigating the correlation of the GS between the biopsy and RP specimens. Pathology error and sampling error are thought to be the main reasons for the discrepancy.

Steinberg et al[11] previously reported that pathologists at an academic center had a better GS correlation than those at community sites. According to their recent study of 1455 patients, Fine and Epstein[6] reported that the exact GS concordance rate was improved in both community sites (from 34% to 70%) and an academic center (multiple pathologists; from 58% to 76%) compared with the rate in their older study. The effects of education and pathologists' efforts in the United States might have contributed to this improvement.

The present study had some differences from that conducted by Fine and Epstein.[6] First, each Gleason pattern was assigned according to the ISUP consensus, which was published in 2005 after their study period (2002-2003). Second, we used the global GS, considering the entire tumor within the prostate as 1 lesion for both the biopsy and the RP specimens because the GS of each core was not available in most (>95%) of the original pathologic reports. The use of the global GS should be considered a weakness of the present study. In the study by Fine and Epstein,[6] the RP GS was recorded from the dominant tumor or highest grade tumor. However, it was not clearly reported whether the global or highest core GS had been used for the biopsy specimens. Although almost all preoperative nomograms have used the highest core grade of the given case when multiple cores with different GSs are present, and urologists have tended to use the greatest GS to determine their treatment plan, some clinicians might use the global GS. ISUP did not actually specify that the highest core GS should be used for the biopsy GS in each case.[2,16,17] Third, the present study included significantly more patients with greater biopsy and RP specimens than the previous study. In the present study, 67% of the biopsy and 74% of the RP specimens had a GS of ≥7 compared with the previous 26% and 23%, respectively.[6,11] This might have resulted from patient selection bias and ethnic differences in the patients with prostate cancer, because the present cohort of patients underwent RP at academic or community institutions in Japan.[18] In addition to the differences in the distribution of GS, the division of GS 7 into 3 + 4 and 4 + 3 might explain the relatively low exact concordance rate in our study. When GS 3 + 4 and 4 + 3 were combined as 1 entity, the exact concordance rate was high (73.6%) in the present study. However, a GS of 3 + 4 and that of 4 + 3 have different biologic behavior and should not be combined into 1 category.[19]

Reflecting contemporary changes regarding prostate cancer and the Gleason grading system, the ISUP proposed a modified Gleason grading system in 2005.[16] The ISUP consensus has been reported to minimize biopsy undergrading and improve the GS correlation compared with the previous system.[12] In the present study, including patients who underwent RP from 1997 to 2005, biopsy GS 2-4 was originally diagnosed at each institution in 14.6% of all patients compared with 1.6% in another study.[6] ISUP recommended that a GS 2-4 should rarely, if ever, be considered, because of the poor correlation with the RP GS. Most expert uropathologists would not have assigned a GS of 2-4 even before the ISUP consensus.[20] In our study, all locally reviewed biopsy GS 2-4 specimens were upgraded by the central review and 61% actually had a RP GS of ≥7, including 3 patients with a RP specimen GS of 8-10. In addition, no RP specimens in the present study was graded with a GS of 2-4. For the GS categories other than 2-4, we also showed that central review using the ISUP consensus gave a more accurate GS correlation than local review, including biopsy GS 8-10. However, the exact concordance rate was far from perfect (100%) and was less satisfactory even when a central review using the ISUP consensus was done. The actual GS of each patient can be apparent only after RP has been performed. We believe this is an advantage for RP compared with other

treatment modalities that offer patient surveillance and adjuvant treatment according to the biopsy GS only.

High-grade Gleason patterns, either a primary/secondary pattern or a tertiary pattern, in RP specimens have been related to a poor outcome.[13-15] We have demonstrated that the central review biopsy GS using the ISUP consensus is superior to the local review biopsy GS in terms of predicting high-grade Gleason patterns in the RP specimens. It has been reported that the highest core GS has the largest effect on a significant upward shift of the biopsy GS among the reporting rules of the ISUP consensus.[21] Because we used a global biopsy GS for the central review, the difference in the interpretation of each Gleason pattern between the local review and central review might explain our results for high-grade Gleason patterns.

CONCLUSIONS

This is the first study to investigate the significance of dedicated pathologic reassessment using the ISUP consensus for biopsy and RP specimens from academic and community practices. Central pathologic review resulted in a more accurate GS correlation and prediction of high-grade Gleason patterns. We believe that more educational effort is needed for both pathology and urology communities to disseminate the ISUP consensus. We recommend central pathology review by dedicated uropathologists for a study of prostate biopsy and RP specimens from patients at multiple institutions, although the central review will cost more and is time-consuming. We should carefully interpret multicenter study data that have not included a central review. In addition, the exact concordance rate was far from perfect (100%) and was not satisfactory even when a central review using the ISUP consensus was done. Also, the actual GS of each patient can be apparent only when RP has been performed.

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Review Article

Combined androgen blockade for prostate cancer: Review of efficacy, safety and cost-effectiveness

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A standard treatment for advanced prostate cancer is androgen deprivation by surgical or medical castration. In theory, however, combined androgen blockade (CAB) with an antiandrogen plus castration should be more effective because castration alone does not completely eliminate androgens in the prostate. Therefore, a number of randomized clinical trials (RCT) were conducted in the 1990s to investigate the efficacy of CAB with an antiandrogen (nilutamide or flutamide) plus castration; however, there were both positive and negative results for the efficacy of CAB. The lack of data on safety, quality of life (QOL) and cost-effectiveness has been a hindrance to the adoption of CAB for the treatment of prostate cancer. Nevertheless, discussion on CAB for the treatment of prostate cancer has continued for over 20 years, which suggests that there remains some hope for this regimen. In the 2000s, clinical research on CAB with the antiandrogen bicalutamide commenced. CAB using this new antiandrogen was found to prolong overall survival (OS) in patients with prostate cancer, with favorable safety profiles and cost-effectiveness, without deteriorating QOL. In this article, we discuss the feasibility of CAB with bicalutamide for the treatment of prostate cancer by reviewing the theoretical background of CAB and then the results of RCT conducted in the 1990s when the usefulness of CAB was assessed. (*Cancer Sci* 2011; 102: 51–56)

Theoretical Background of CAB

Huggins *et al.*[1] first reported the effects of hormonal therapy on metastatic prostate cancer about 70 years ago. Since then, several studies have examined the efficacy of hormonal therapy for this disease. However, results from these earlier studies were probably not optimal because few drugs were available and the disease was mostly advanced before the prostate-specific antigen (PSA) test was available for screening. Therefore, these data with older drugs could have disguised the benefits of CAB described in a later section. It has been reported that prostate cancer is androgen-dependent in the majority of cases and that 95% of androgens are testosterone of testicular origin.[2] These androgens are thought to promote the growth of cancer cells by binding to androgen receptors (AR) in prostate cancer cells. Therefore, the first-line treatment for advanced prostate cancer has been androgen deprivation by medical castration with luteinizing hormone-releasing hormone agonist (LHRH-A) or by surgical castration with bilateral orchiectomy.

However, it has been shown that dehydroepiandrosterone (DHEA) and androstenedione are also converted to androgens in prostate cancer cells after secretion from the adrenal glands.[3] Therefore, it is expected that blockade of androgen of adrenal origin by an antiandrogen, which inhibits the binding of androgen to AR, combined with castration could lead to more effective inhibition of prostate cancer.[4] Thus, since the end of the 1970s, CAB has been investigated as a potential treatment for prostate cancer. It has been reported that nonsteroidal antiandrogens show favorable efficacy profiles and are well-tolerated, and that antiandrogens with a higher AR affinity have stronger androgen-suppressive effects.[5–7]

Usefulness of CAB *Versus* Castration Alone

In the 1990s, approximately 30 were conducted to investigate the efficacy and safety of CAB compared with castration alone.

Crawford *et al.*[8] studied the efficacy of CAB in 603 patients with stage D2 prostate cancer after being randomized to treatment with leuprorelin (a LHRH-A) plus placebo or flutamide. They showed that the progression-free survival (PFS) was significantly prolonged in the flutamide group compared with the placebo group at 16.5 *vs* 13.9 months ($P = 0.039$). Additionally, the median survival was 35.6 months in the flutamide group and 28.3 months in the placebo group, which was significantly better in the flutamide group ($P = 0.035$). Although tolerability was similar in both groups, the incidence of moderate diarrhea was significantly greater in the flutamide group ($P < 0.001$).

Boccardo *et al.*[9] randomized 373 patients with stage C or D prostate cancer to treatment with goserelin (a LHRH-A) alone, or CAB with goserelin plus flutamide. At a median follow up of 24 months no significant differences were observed in response rates, PFS or overall survival (OS) between the groups. Although the median time to progression (TTP) was 18 months in the goserelin group and 24 months in the CAB group, the difference was not statistically significant ($P = 0.09$). In addition, the time to normalization of serum prostatic acid phosphatase concentrations and the time to relief of bone pain were shorter in the CAB group than the goserelin alone group, whereas the incidence of adverse reactions such as diarrhea and increased blood transaminases was significantly higher in the flutamide group than the goserelin alone group.

Eisenberger *et al.*[10] randomized 1387 patients with metastatic prostate cancer to bilateral orchiectomy plus placebo or the antiandrogen flutamide. The median follow-up time was 49.2 months in the placebo group and 50.1 months in the flutamide group. The OS did not differ significantly between the two groups ($P = 0.14$) and there was no significant reduction in the risk of death in the flutamide group compared with the placebo group (hazard ratio [HR] = 0.91; 95% confidence interval [CI] = 0.81–1.01). Although the incidence of toxicity associated with both treatments was generally low, grade 2 or higher diarrhea and anemia were significantly more frequently observed in the flutamide group than the placebo group ($P = 0.002$ and $P = 0.024$, respectively).

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Dijkman *et al.*[11] reported the clinical results of 457 patients with stage D2 prostate cancer randomized to treatment with the antiandrogen nilutamide or placebo following orchiectomy; follow up was approximately 8.5 years. The proportion of patients who achieved normalization of the PSA level after 3 months of treatment was significantly higher in the nilutamide group than the placebo group ($P < 0.001$). Additionally, TTP was significantly prolonged in the nilutamide group at 21.2 months *versus* only 14.7 months in the placebo group ($P = 0.002$). Moreover, median cancer-specific survival was significantly prolonged in the nilutamide group at 37.0 months *versus* only 29.8 months in the placebo group ($P = 0.013$).

These four studies were the most notable RCT conducted in the 1990s, and they showed both positive and negative efficacy results for CAB using nilutamide and flutamide for the treatment of prostate cancer. Therefore, it remains unclear and questionable as to whether the strategy of CAB is superior to castration alone.

To help clarify these data, the Prostate Cancer Trialists' Collaborative Group (PCTCG)[12] conducted a meta-analysis of 27 RCT that involved a total of 8275 patients with advanced prostate cancer. The efficacy of surgical or medical castration alone was compared with that of CAB using a steroidal antiandrogen (cyproterone acetate) or a non-steroidal antiandrogen (flutamide or nilutamide). The 5-year survival rate was 25.4% in the CAB group and 23.6% in the castration alone group, which was not significantly different (log-rank $2P = 0.11$). However, when the data were stratified by the type of antiandrogen, the 5-year survival rate in patients receiving CAB with a non-steroidal antiandrogen (flutamide or nilutamide) was found to be significantly superior to that of patients receiving castration alone: 27.6% *vs* 24.7%, respectively (log-rank $2P = 0.005$) (Fig. 1). It should be noted that the non-steroidal antiandrogens used in the analysis were flutamide and nilutamide, because bicalutamide – currently the leading antiandrogen – was not available at that time.

Thus, although there was a theoretical justification for using CAB for prostate cancer, the survival benefit observed compared with castration alone in RCT and meta-analyses in the 1990s was small. In addition, the data did not demonstrate the superiority of CAB *versus* castration alone with respect to safety profiles, QOL and cost-effectiveness. Therefore, there was insufficient evidence to recommend CAB strongly at that time. Indeed, the 2004 American Society of Clinical Oncology (ASCO) Recommendations for the Initial Hormonal Management of Androgen-Sensitive Metastatic, Recurrent or Progressive Prostate Cancer[13] evaluated these strategies in terms of benefit, harm and cost, and concluded that "a small survival advantage was likely with CAB over castration alone, although the benefit must be balanced against great toxicity and extraordinarily poor cost-effectiveness."

Evaluation of CAB with Bicalutamide

As mentioned, data on CAB from the 1990s have not established its superiority over castration alone, with regard to efficacy, safety, QOL or cost-effectiveness. By the late 1990s, CAB with bicalutamide had been frequently evaluated to assess the usefulness of CAB.

Efficacy. Schellhammer *et al.*[14] studied 813 patients with stage D2 prostate cancer after randomization to treatment with either LHRH-A plus bicalutamide or flutamide. They showed that the median TTP was 97 weeks in the bicalutamide group and 77 weeks in the flutamide group, and that the median survival was 180 weeks in the bicalutamide group and 148 weeks in the flutamide group. Although bicalutamide prolonged both TTP and median survival, the differences between the two groups were not significant ($P = 0.41$ and $P = 0.15$, respectively) (Fig. 2). Re-analysis by Klotz *et al.*[15] found that CAB with 50 mg bicalutamide reduced the risk of death by 20% compared with castration alone (Fig. 3), through careful evaluation of disparate trials which is called "delta-method". However, there are several limitations to cross-study comparisons and the lack of data from an RCT that has compared bicalutamide-containing CAB *versus* castration alone leaves room for discussion of the benefits of this combination therapy.

A phase III randomized, double-blind, placebo-controlled trial[16,17] was conducted with 205 Japanese patients with stage C or D prostate cancer, who were randomized to either CAB with LHRH-A plus bicalutamide or LHRH-A monotherapy. Over a median observation period of 2.4 years, there was significant prolongation of TTP and the time to treatment failure (TTTF) in the CAB group compared with the LHRH-A monotherapy group ($P < 0.001$). Therefore, further follow up was conducted to investigate the survival outcome (Fig. 4).[18] After a median follow up of 5.2 years[19] a significant OS advantage was observed with CAB *versus* LHRH-A monotherapy (HR = 0.78; 95% CI = 0.60–0.99; $P = 0.0498$) (Fig. 5). Indeed, the 5-year OS rate estimated by the Kaplan–Meier method was 75.3% in the CAB group and 63.4% in the LHRH-A monotherapy group. A subgroup analysis of OS by disease stage[19] revealed that the survival rate of stage C or D1 patients was significantly higher in the CAB group than in the LHRH-A monotherapy group ($P = 0.0041$). However, in stage D2 patients no significant difference was observed in the survival rate between the study arms ($P = 0.8335$). In addition, no significant differences were observed between the groups in relation to cause-specific survival. This suggests that CAB is more effective in prostate cancer patients with early stage disease, such as C and D1. The proportion of patients who achieved a PSA nadir of ≤1 ng/mL was significantly different between the groups, with 81.4% of patients in the CAB group achieving that end-point *versus* only 33.7% in the LHRH-A monotherapy group ($P < 0.001$).[19] The investigators found in an exploratory analysis that achieving a PSA nadir of ≤1 ng/mL was a significant prognostic factor for improved OS. These data support the findings of Klotz *et al.*[15] that CAB with bicalutamide improved survival by approximately 20% compared with surgical or chemical castration alone.

Although de Leval *et al.*[20] and Sato *et al.*[21] have reported data suggesting a role for intermittent therapy, no consensus about methodology and efficacy has yet been reached. Therefore, intermittent CAB therapy for advanced prostate cancer should be investigated only in clinical research.

Safety and QOL. Usami *et al.*[17] compared safety outcomes in the previously mentioned RCT between the CAB and LHRH-A monotherapy groups after 2.4 years of follow up. They found that the dropout rate due to adverse drug reactions (ADR) was 8.8% in the CAB group and 10.9% in the LHRH-A monotherapy group (95% CI = 6.4–10.7). In addition, tolerability profile, overall ADR (66.7% for CAB and 65.3% for LHRH monotherapy) and adverse events (93.1% for both groups) was similar in both groups. Arai *et al.*[22] compared QOL between the CAB group and the LHRH-A monotherapy group using the Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaire. They reported that there was no decrease in overall QOL in the CAB group, but rather the CAB group had more rapid and greater improvements in "emotional well-being" and "prostate cancer-specific issues" domain scores in FACT-P compared with the LHRH-A monotherapy group. Additionally, they showed that CAB improved micturition disorder-related QOL – a factor that greatly contributed to an improvement in the "prostate cancer-specific issues" domain.

With regard to the effect of CAB on cardiovascular risk, three scientific societies – the American Heart Association, American

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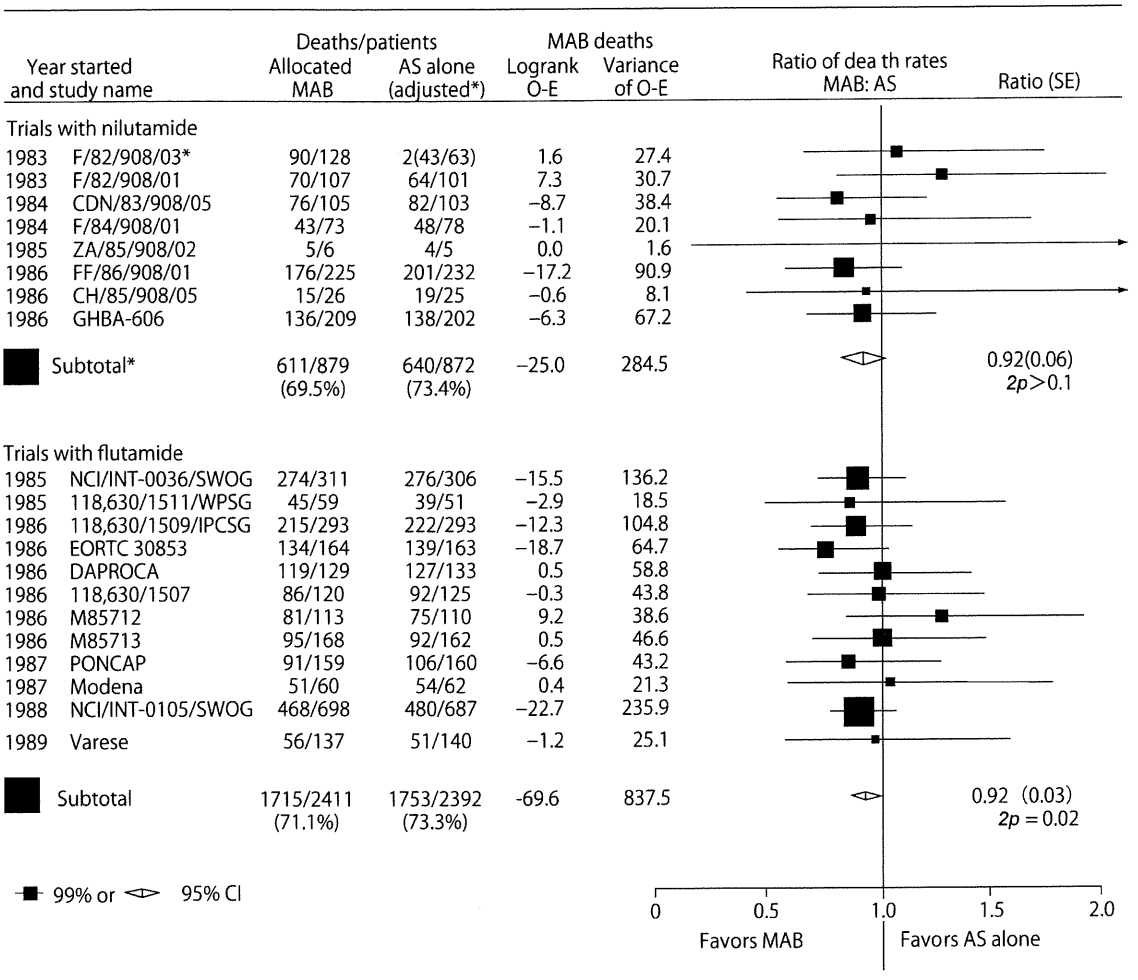

Fig. 1. Mortality results from randomized trials of maximal androgen blockade (MAB) *versus* androgen suppression (AS) alone in advanced prostate cancer. The black squares indicate the ratio of daily death rates (MAB *vs* AS), as calculated from the log rank statistics, and the horizontal line gives the corresponding 99% confidence interval (CI). The area of the square is proportional to the amount of information it represents. Ratios less than 1.0 favor MAB and ratios more than 1.0 favor AS alone. A diamond is used to denote the corresponding result and its 95% CI for the total of all trials (and for subtotals). *Adjusted = for balance, control patients in three-way trials count half or twice in subtotals and in the final totals of deaths and patients. O–E, Observed minus Expected. Adapted from the Prostate Cancer Trialists' Collaborative Group, with permission.[12]

Cancer Society and American Urological Association – have jointly proposed guidelines on hormonal therapy for prostate cancer and cardiovascular risk.[23] The guidelines include a statement that "at present, it is appropriate to consider that androgen deprivation may be associated with cardiovascular events and cardiovascular death," based on research reports that androgen deprivation for prostate cancer causes weight gain, a decrease in insulin sensitivity and lipid metabolism abnormalities. In light of these data, the guidelines recommend monitoring blood pressure lipid and blood glucose levels before starting androgen deprivation therapy and within 3–6 months after the start of therapy. In addition, for patients on long-term androgen deprivation therapy, the guidelines recommend monitoring lipid and blood glucose levels at least once a year.

In Japan, the number of patients with cardiovascular disease is lower than in Western countries. Even though the consumption of fat and the average total serum cholesterol level have increased in Japan, rates of mortality and morbidity from myocardial infarction remain the lowest of all developed countries.[24] These observations are supported by findings from the WHO multinational monitoring of trends and determinants in cardiovascular disease (The WHO MONICA project),[25] which monitors trends in cardiovascular diseases and related risk factors.

Akaza *et al.*[26] have reported that the expected life years of patients with localized or locally advanced prostate cancer after hormonal therapy or surgical castration are similar to those of the general population. The results of a search of a large database, introduced in the review article by Akaza *et al.*[27] (Table 1), also support this finding. However, at this time, because no definite conclusion has been reached about the relationship between androgen deprivation therapy and cardiovascular risk, it might be preferable to monitor patients with cardiovascular complications on a regular basis.

No RCT has been conducted on the fracture risk with CAB; however, Bolla *et al.*[28] have reported a fracture risk with hormonal therapy after external beam radiotherapy. In their study, 415 patients with advanced prostate cancer received the LHRH-A goserelin for 3 years after external beam radiotherapy and pathological fracture was observed in only two patients.

These studies suggest that the effects of hormonal therapy on bone metabolism and cardiovascular risk in patients with

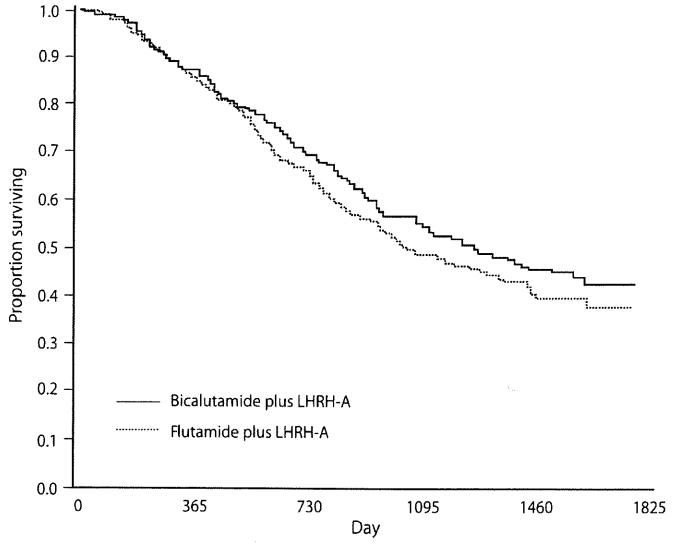

Fig. 2. Kaplan–Meier distributions of survival time comparing CAB with bicalutamide and CAB with flutamide. LHRH-A, luteinizing hormone-releasing hormone agonist. Adapted from Schellhammer *et al.*, with permission.[14]

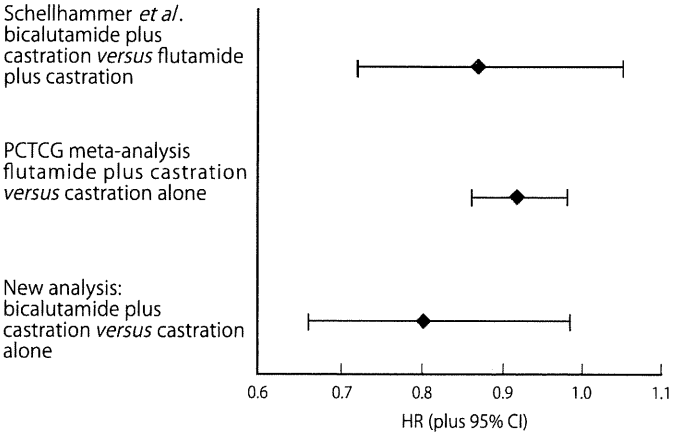

Fig. 3. Hazard ratios (HR) for OS. CI, confidence interval. Adapted from Klotz *et al.*, with permission.[15]

prostate cancer do not outweigh the benefits of hormonal therapy. Therefore, it is recommended that health care providers discuss both the risks and benefits of CAB with bicalutamide with patients prior to the selection of a treatment approach.

Cost effectiveness. To address the issue of cost-effectiveness, Nishimura *et al.*[29] constructed a Markov model that examined the prognosis of untreated prostate cancer and estimated the cost-effectiveness of CAB in comparison with that of LHRH-A monotherapy. The model showed that the expected costs of CAB and LHRH-A monotherapy were 5.24 and 3.66 million yen (approximately US$55 851 and US$39 010), respectively, with expected survival durations of 7.45 and 6.44 years, respectively. The incremental cost-effectiveness ratio (ICER) for CAB compared with LHRH-A monotherapy was 1.56 million yen/life-year-saved (approximately US$16 627), and was lower than the ICER threshold set in the study (6 million yen/life-year-saved [approximately US$63 952]), which demonstrates that the cost-effectiveness of CAB is superior to that of LHRH-A monotherapy. Similar results were found in a study conducted by Penson *et al.*[30]

CAB Conclusion

As described in this review, CAB for prostate cancer has been investigated in many RCT and in meta-analyses since the 1990s. However, its role in the treatment of prostate cancer has been debated due to the contradictory results from these trials. Therefore, the 2004 clinical practice guidelines issued by ASCO concluded that CAB confers a statistically significant but questionable clinical improvement in survival over orchiectomy or LHRH-A monotherapy. However, more recently, the efficacy and safety of CAB have been investigated using the antiandrogen bicalutamide. Data from these trials suggest that CAB with bicalutamide significantly prolongs survival without deteriorating safety and QOL[16–19,22] in Japanese patients with prostate cancer. These data might be supported by the results that Fukagai *et al.*[31] reported in 2006, which suggested racial differences between Japanese and Caucasians as a factor for the differences in clinical outcomes after hormonal therapy. Therefore, after evaluating these data,[15,16] ASCO revised its recommendations[32] for hormonal therapy for prostate cancer in 2007 as follows: ''Given that the bicalutamide CAB has minimal, if any, additional toxicity over castrate therapies alone and is significantly cheaper than the newer systemic therapies, until the results of a trial designed to address the potential survival benefit is available, patients should be made aware of the findings described herein, and bicalutamide CAB should be considered.''

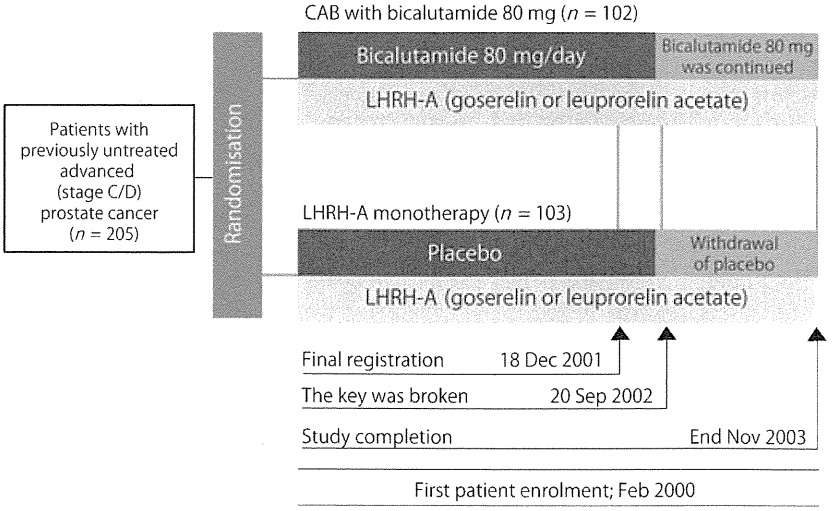

Fig. 4. Study design comparing CAB with bicalutamide and LHRH-A monotherapy.[17] Adapted from Hinotsu *et al.*, with permission.[18]

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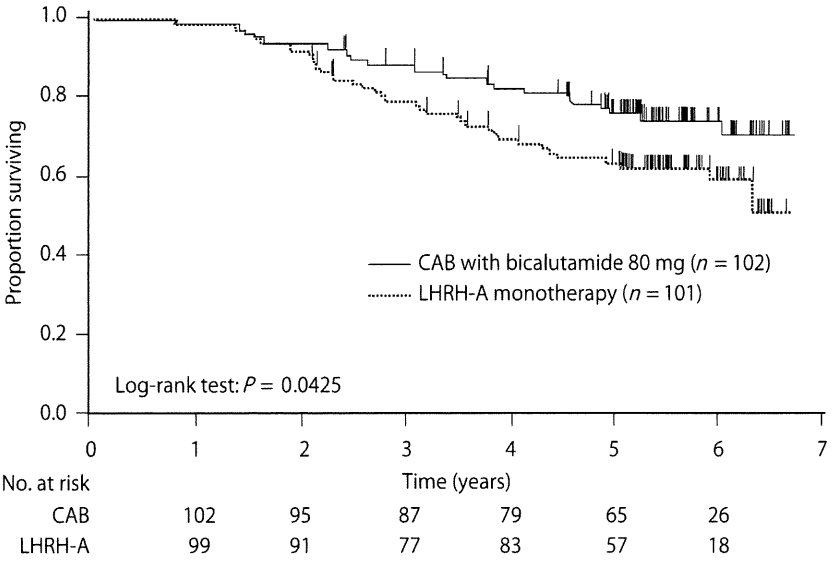

Fig. 5. Kaplan–Meier curve of overall survival comparing CAB with bicalutamide and LHRH-A monotherapy.

Table 1. Cardiovascular deaths among leuprorelin-treated patients compared with a similar-sized general Japanese population cohort in the years 2001–2006 (data from Japan study group of Prostate Cancer [J-Cap])

Year	Observed number of leuprorelin-treated patients	CV deaths in leuprorelin-treated patients	Estimated CV mortality rate/ Japanese general population cohort
2001	800	2	4.0/800
2001	1666	5	9.1/1666
2003	2515	16	15.1/2515
2004	2243	9	14.5/2243
2005	1835	10	12.7/1835
2006	1470	7	11.0/1470

CV, cardiovascular. Adapted from Akaza *et al.*, with permission.[27]

Additionally, the cost-effectiveness of CAB with bicalutamide has been shown to be excellent, when considering its overall survival benefit.[29,30] Thus, recent data have shown that CAB, a strategy which has been debated for many years, is a viable treatment option for prostate cancer when bicalutamide is used as the antiandrogen for CAB.

Discussion

In conclusion, CAB with bicalutamide is gaining support due to the publication of the ASCO 2007 guidelines and the Akaza *et al.*[19] trial. In addition, new hormonal drugs are being developed, including an LHRH antagonist (degarelix), selective CYP17 inhibitors (abiraterone and TAK700) and MDV3100, which is said to be a second-generation oral antiandrogen. In addition, in castration-resistant prostate cancer, which has recently been gaining attention, Cheng *et al.*[33] have suggested the involvement of AR in the growth of cancer cells. Therefore, the role of hormonal therapy using drugs with pharmacological effects via androgens is gaining attention for the treatment of prostate cancer. It remains to be seen how CAB will compare with castration alone and other potential therapies when these new drugs become available.

Disclosure Statement

The authors have no conflict of interest.

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Original Articles

Phase III Trial of Everolimus in Metastatic Renal Cell Carcinoma: Subgroup Analysis of Japanese Patients from RECORD-1

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Objective: To assess the efficacy and safety of everolimus in Japanese patients with metastatic renal cell carcinoma.
Methods: A subgroup analysis of the pivotal Phase III, randomized, double-blind, placebo-controlled trial of everolimus 10 mg/day in patients with disease progression after treatment with sorafenib, sunitinib or both assessed outcomes in Japanese participants. Results were compared with those for the overall study population.
Results: The final trial analysis included 24 Japanese patients (everolimus, $n = 15$; placebo, $n = 9$). Median progression-free survival in the Japanese subpopulation was 5.75 months (95% confidence interval, 4.90 months to not reached) with everolimus and 3.61 months (95% confidence interval, 1.91–9.03 months) with placebo (hazard ratio, 0.19; 95% confidence interval, 0.05–0.83). Median overall survival was not reached with everolimus and was 14.9 months (95% confidence interval, 11.0–16.8 months) with placebo (hazard ratio, 0.30; 95% confidence interval, 0.07–1.27). Overall, efficacy and safety were similar when comparing the Japanese and overall populations. In the Japanese subpopulation, the most common adverse events with everolimus were stomatitis, infections and rash. Four Japanese subjects (27%) developed Grade 1 ($n = 2$) or 2 ($n = 2$) pneumonitis (all reversible and allowing for continuation of therapy, after interruption, steroids and dose reduction for both Grade 2 cases), with a lower pneumonitis incidence of 14% in the overall population (albeit associated with a Grade 3 incidence of 4%).
Conclusions: These findings suggest that the demonstrated benefits of everolimus in the overall trial population are similar in Japanese patients with metastatic renal cell carcinoma.

Key words: everolimus – renal cell carcinoma – mTOR

INTRODUCTION

The incidence of renal cell carcinoma (RCC) in Japan is increasing. Results of a survey conducted from January 2002 through December 2002 in all 47 prefectures revealed the crude incidence rates of RCC to be ~8.2 males and 3.6 females per 100 000 persons, an increase of ~1000