ONCOLOGY REPORTS 25: 57-62, 2011

Characteristics of severe adverse events after peptide vaccination for advanced cancer patients: Analysis of 500 cases

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Received July 21, 2010; Accepted September 16, 2010

DOI: 10.3892/or_00001041

Abstract. The purpose of this study was to investigate severe adverse events (SAEs) after therapeutic peptide vaccination for advanced cancer patients. We investigated SAEs following personalized peptide vaccinations in 500 advanced cancer patients, including 174 prostate, 74 colon, 51 pancreatic and 43 gastric cancer patients. The number of vaccination cycles varied widely, from 3 to 112. The severity of adverse events was scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3, and events with a grade of >3 were defined as SAEs and were evaluated by the Institutional Safety Evaluation Committee. A total of 215 SAEs in 102 patients were recorded during the vaccine trials. The main causes for these events were cancer progression (152 SAEs in 78 patients), combined cancer treatments other than vaccination (35 in 21 patients), diseases other than cancer (20 in 19 patients), peptide vaccines (6 in 6 patients) and suicide (1 in 1 patient). The 6 vaccine-related SAEs, all grade 3, consisted of skin reactions at each injection site, cellulitis around the injection site, edemas of the head and neck regions, colitis, rectal bleeding and bladder-vaginal fistulae. Both cellular and humoral responses to the vaccinated peptides were highly boosted in all 6 of these patients, indicating the involvement of augmented immune responses in these SAEs. The clinical responses in these 6 patients consisted of 2 partial responses and 4 stable diseases. The majority of SAEs after peptide vaccination for advanced cancer patients were caused by cancer progression. The appearance of vaccine-related SAEs, except inflammatory injection site reactions, was unexpected, and fortunately the incidence was very low. Our results suggest that physicians should be on guard for these rare SAEs associated with augmented immune responses.

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Key words: severe adverse events, peptide vaccine, advanced cancer

Introduction

The field of therapeutic cancer vaccines for advanced cancer patients is currently in an active state of clinical investigations. Many clinical trials of therapeutic cancer vaccines have demonstrated their tolerability, based on the absence or rarity of severe adverse events (SAEs) caused by the vaccination (1-10). To our knowledge, however, there has been no detailed study of SAEs after therapeutic peptide vaccines. Indeed, certain randomized trials of tumor cell-based or idiotype vaccines have shown a detrimental effect on the vaccine arm, suggesting that cancer vaccines are not always safe (11-13).

In order to better understand the safety of cancer vaccines, we analyzed the records of a total of 500 advanced cancer patients who received personalized peptide vaccinations between October 2000 and October 2009. SAEs other than injection site reactions were rare, but were also documented.

Materials and methods

Patients. Between October 2000 and October 2008, 500 patients positive for HLA-A24, -A2, or -A3 supertypes with various types of advanced cancer took part in phase I, I/II and II studies for personalized peptide vaccinations after providing their written informed consent. The advanced cancers originated from the prostate (n=174 patients), colon and rectum (n=74), pancreas (n=51), stomach (n=43), brain (n=34), uterus (n=28), lung (n=22), kidney (n=13), skin (n=12), breast (n=11), bladder and urinary tracts (n=10), or other locations (n=29). The patient characteristics and HLA types for vaccination, are shown in Table I. These studies were undertaken at 10 different institutions (Kurume University Hospital, Kinki University Hospital, Okayama University Hospital, Nara Medical University Hospital, Hokkaido University Hospital, Niigata University Hospital, Kitasato

Table I. Severe adverse events observed in the clinical trials of the personalized peptide vaccination.

			SAE				
				Event no.			
Disease	n	Median age years	Observed case no.	Total	Grade 3	Grade 4	Grade 5
Prostate cancer	174	67.9	55	95	73	11	11
Colorectal cancer	74	58.5	5	6	1	1	4
Pancreatic cancer	51	64.8	20	81	65	3	13
Gastric cancer	43	58.7	1	1	0	0	1
Malignant brain tumor	34	49.6	2	2	1	1	0
Cervical cancer	28	49.9	3	5	5	0	0
Non-small cell lung cancer	23	60.5	2	2	1	0	1
Renal cell cancer	13	57.8	2	2	2	0	0
Melanoma	12	57.3	1	1	0	0	1
Breast cancer	11	54.3	3	4	3	0	1
Bladder cancer	8	66.6	5	6	1	3	2
Others	29	63.6	3	10	6	2	2
Total	500	61.8	102	215	158	21	36

University Hospital, Kansai Medical University Hirakata Hospital, Yamaguchi University Hospital, and Kyoundo Hospital in Japan), and were approved by the ethics review committee of each institution. The number of administered vaccinations varied widely, from 3 to 112 per patient, with the most prolonged vaccination periods being for the prostate cancer patients. Most of the safety, immune, as well as clinical responses in these studies have been previously reported (5-10,14-25). Studies are currently underway to obtain vaccination results for the treatment of pancreatic and breast cancer, as well as for the HLA-A3 supertype-positive patients. Results obtained after October 2008 have not been included in this study (unpublished data). The detailed patient characteristics of the 500 patients, including their immunological responses and clinical evaluations, are also currenlty being studied for the purpose of identifying biomarkers to predict clinical benefits (Noguchi *et al*, unpublished data).

Treatment regimens. Personalized peptide vaccination is based on a pre-vaccination measurement of the peptide-specific CTL precursors and anti-peptide IgG in the circulation of cancer patients, reactive to vaccine candidates, followed by the administration of only reactive peptides (up to 4 peptides) with Freund's incomplete adjuvant (ISA51; Seppic, Paris) as reported previously (5-10). A total of 78 candidate peptides (32 peptides for HLA-A24, 37 for -A2 and 8 for -A3 supertype-positive patients) were used in the personalized peptide vaccination (5-10). All of these peptides can induce the HLA-A24, A2- and -A3 supertype-restricted and tumor-specific CTL activity in the peripheral blood mononuclear cells (PBMCs) of cancer patients.

Physical examinations and baseline blood tests were repeated at 2-week intervals, and patients were questioned about adverse events, including their severity and frequency. The severity of adverse events was scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3 (2003). The SAEs were evaluated by the Institutional Safety Evaluation Committee (ISEC). Imaging studies to determine the extent of disease were performed at intervals of 3 months and repeated after 3 to 6 months to identify patients with responses. Patients were assigned a response category according to the Response Evaluation Criteria in Solid Tumors, the revised version of the WHO criteria published in the WHO Handbook for Reporting Results of Cancer Treatment, June 1999 (Final).

Results

SAEs. A total of 215 SAEs in 102 patients and their grades were recorded during the vaccination (Table I). There were 158 grade 3, 21 grade 4, and 36 grade 5 SAEs. The main causes for these events were cancer progression (152 SAEs in 78 patients), combined cancer treatments other than vaccination (35 SAEs in 21 patients), diseases other than cancer (20 SAEs in 19 patients), peptide vaccines (6 SAEs in 6 patients), and suicide (1 in 1 patient). The frequencies of SAEs were high in the bladder, pancreas and prostate cancer patients, whereas they were low in the gastric and colon cancer patients, and also in patients with malignant brain tumors.

The 6 vaccine-related SAEs, all grade 3, consisted of skin reactions at each injection site, cellulitis around the injection site, edemas of the head and neck regions, colitis, rectal bleeding and bladder-vaginal fistulae (Table II). Each of these cases is briefly described in the next section.

Case reports of the vaccine-related SAEs. Grade 2 inflammatory skin reactions at the injection sites (thigh regions)

Vaccine-related severe adverse events.

Case ID	Age at entry	Gender	Disease	Total no. of vaccinations	Onset of SAE (vaccination times)	SAE	CTCAE grade	Clinical outcomes		
								BCR	PFS	OS
K-GEM-005	73	F	Pancreatic cancer	77	48	Dermatology/ skin-other (cellulitis)	3	SD	803	1123
K-GEM-008	54	M	Pancreatic cancer	23	19	Injection site reaction-ulceration	3	SD	153	362
EBO-112P	77	M	Prostate cancer	104	102	Edema: Head and neck	3	PR	437	2430
EBL-002	61	M	NSCL	23	7	Colitis	3	SD	323	668
EBG-101	68	F	Cervical cancer	10	10	Hemorrhage, GI-rectum	3	PR	323	323
GY-II-004	75	F	Cervical cancer	29	25	Fistula, GU-bladder/ vagina	3	SD	789	804

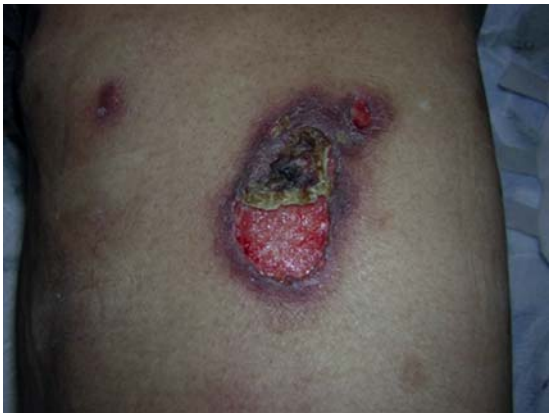

Figure 1. A skin ulcer at the injection site. Grade 3 ulcerations appeared at the previous injection sites of the thigh regions after the 19th vaccination in the abdominal region, in a patient with advanced pancreatic cancer (K-GEM-008).

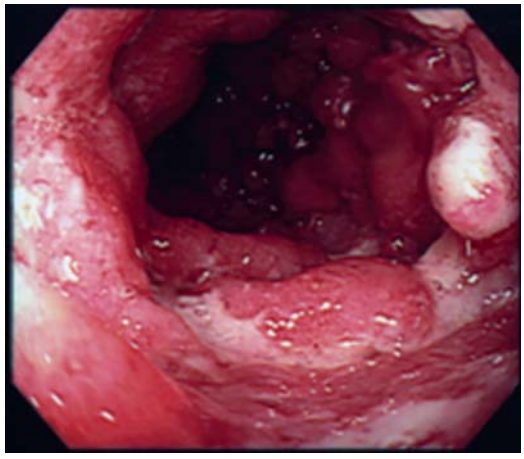

Figure 2. Colitis associated with ulcers. Examination with a sigmoid fiberscope revealed colitis associated with ulcers in a patient with advanced non-small cell lung cancer (EBL-002).

appeared after the 29th vaccination in a 73-year-old female patient with advanced pancreatic cancer (K-GEM-005, stage IVb), and therefore the vaccination interval was extended from 2 to 3 weeks in this patient (Table II). However, grade 3 cellulitis appeared at the injection site after the 48th vaccination in this patient, and consequently both the vaccination and gemcitabine were terminated for 4 weeks. After the disappearance of cellulitis, the vaccination and gemcitabine were resumed and continued until the 77th vaccination. The best clinical response (BCR) was stable disease (SD) with a progression free survival (PFS) of 803 days and an overall survival (OS) of 1123 days.

Grade 2 inflammatory skin reactions at the injection sites (the thigh regions) appeared after the 15th vaccination in a 54-year-old male patient with advanced pancreatic cancer (K-GEM-008, stage IVb), and consequently the injection sites were changed from the thigh to the side-abdominal regions (Table II). However, grade 3 ulcerations appeared at the previous injection sites in the thigh regions after the 19th vaccination. The clinical trial was terminated after the 23rd vaccination due to the skin ulcers in the thigh regions. The BCR was SD with a PFS of 186 days and an OS of 362 days. A representative ulcer at the injection site is shown in Fig. 1.

Grade 3 edema of the head and neck regions appeared 6 days after the 102nd vaccination in the subcutaneous thigh regions in a 77-year-old male patient with advanced hormone refractory prostate cancer (EBO-112P) who had been

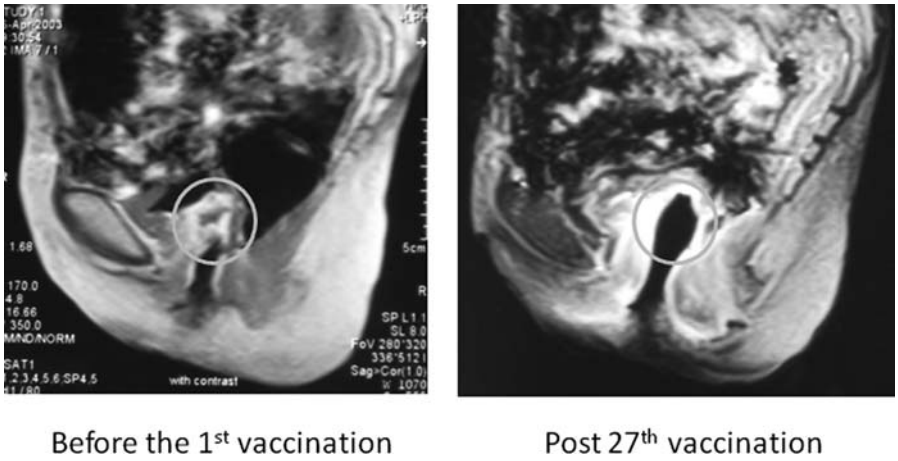

Figure 3. Bladder-vaginal fistula. Magnetic resonance imaging revealed the disappearance of the tumor mass after the 27th vaccination in a patient with advanced cervical cancer (GY-II-004).

responding well to the vaccination for a long period of time (Table II). The ISEC permitted the continuation of the vaccination therapy with careful observation, so the patient received the 103rd vaccination 14 days after the 102nd vaccination. Grade 3 edema of the head and neck region re-appeared 13 days after the 103rd vaccination. The patient was hospitalized for treatment, and the edema disappeared thereafter. The vaccination was terminated after the 104th vaccination based on the recommendations of the ISEC. The BCR was a partial response (PR) with a PFS of 437 days and an OS of 2430 days.

Grade 2 diarrhea appeared in a 61-year-old male patient with advanced non-small cell lung cancer (EBL-002, stage IVb), after the 4th vaccination (Table II). The diarrhea became more frequent after the 5th vaccination, and the vaccination interval was prolonged from 2 to 4 weeks. Examination with a sigmoid fiberscope revealed localized colitis. As the patient experienced no diarrhea thereafter, the interval was shortened again to 2 weeks after the 17th vaccination. Grade 3 diarrhea appeared after the 19th vaccination, and the vaccination interval was again prolonged from 2 to 4 weeks. However, the diarrhea and associated rectal bleeding continued. Examination with a sigmoid fiberscope revealed colitis associated with ulcers (Fig. 2). The patient was hospitalized for treatment, and the symptoms disappeared thereafter. The vaccination was terminated after the 23rd vaccination based on the recommendations of the ISEC. The BCR was SD with a PFS of 323 days and an OS of 668 days.

Constipation and rectal narrowing appeared after the 5th vaccination in a 68-year-old female patient with advanced cervical cancer (EBG-101, stage IV) who had a history of whole pelvic radiation therapy (60 Gy). A colostomy was carried out based on the diagnosis of radiation colitis. The patient re-entered the clinical trial. Grade 3 rectal bleeding with anemia appeared after the 7th vaccination, and blood transfusion was required in order to continue the treatment. Examination with a colon fiberscope revealed redness and swelling of the rectal mucosa, and a diagnosis of radiation colitis was made again. No invasion of cancer cells was observed. The ISEC concluded that the rectal bleeding was mainly caused by radiation colitis, and the vaccination therapy was considered not to have played a role. The dose of vaccination was reduced from 3 to 1 mg/peptide based on the recommendations of the ISEC. The rectal bleeding disappeared thereafter. The BCR was PR with an OS of 323 days. The patient died as a result of sepsis due to pyelonephritis, but not due to the progression of cancer.

Incontinence of urine appeared after the 24th vaccination in a 75-year-old female patient with advanced cervical cancer (GY-II-004, stage IV) who had a history of whole pelvic radiation therapy (60 Gy), and was diagnosed as a bladder-vaginal fistula. The tumor mass disappeared after the 27th vaccination (Fig. 3). The ISEC concluded that the fistula was mainly caused by vaccination-induced anti-tumor responses at the tumor sites, but the involvement of radiation colitis was not excluded. The vaccination was terminated after the 29th vaccination based on the recommendations of the ISEC. The BCR was SD with a PFS of 789 days and an OS of 806 days.

Immune responses and clinical responses at the onset of SAE. We next examined whether boosted immune responses were truly involved in the 6 cases of vaccine-related SAEs (Table II). Both CTL responses and IgG responses to each of the vaccinated peptides around the onset of SAEs, are shown in Table III. Both CTL and IgG responses to at least 2 peptides were observed in all patients. CTLs to all 4, 3, or 2 peptides were observed in 3, 1, or 2 patients in quadruplicate assays, respectively. All 4 out of 4 wells tested positive for 4 patients, while 3 out of 4 wells tested positive for 3 patients, indicating that the CTL precursor frequencies in post-vaccination PBMCs around the onset of the vaccine-related SAEs were much higher than those in the pre-vaccination PBMCs. Furthermore, the amounts of IFN-γ exceeded 500 ng/ml in most wells for all patients, suggesting the elevating activity of peptide-specific CTLs. Similarly, IgG responses to the vaccinated peptides were observed in 5 out of 6 patients. In addition, the IgG titers in post-vaccination plasma increased >100-fold in these 5 patients compared to those in pre-vaccination plasma. These results

Antigen-specific CTL and IgG responses to the vaccinated peptides at the time of SAE onset.

Case ID	Vaccinated peptides	IFN-γ production (pg/ml)[a]		NIgG (FIU)[b]	
		Pre-vaccination	SAE onset	Pre-vaccination	SAE onset
K-GEM-005	SART3-109	- (0)	- (0)	130	20,936
	Lck-486	- (0)	1419, 553 (2)	69	1,116
	PTHrp-102	- (0)	- (0)	113	14,500
	EZH2-291	- (0)	2266, 1075, 684, 381 (4)	10	29
K-GEM-008	SART3-109	- (0)	299 (1)	184	3,929
	Lck-486	- (0)	- (0)	62	161
	HER2/neu-553	47 (1)	553, 190, 133 (3)	20	24,555
	PTHrp-102	- (0)	- (0)	36	38
EBO-112P	SART3-309	359, 130 (2)	4076, 2691, 2102, 1324 (4)	10	23,960
	Lck-246	136, 100 (2)	2950, 2198, 1197 (3)	25	26,434
	UBE2V-43	- (0)	876 (1)	120	26,231
	UBE2V-85	- (0)	>5000, >5000 (2)	113	20,258
EBL-002	SART2-93	123 (1)	262, 190, 123, 96 (4)	<10	<10
	SART3-315	336 (1)	269 (1)	<10	<10
	Lck-208	100, 65 (2)	229, 118, 77, 52 (4)	<10	<10
	Lck-486	112 (1)	257, 123, 96 (3)	<10	<10
EBG-101	Lck-422	142 (1)	>5000, >5000, 905, 842 (4)	<10	<10
	MAP-432	130, 103, 41 (3)	>5000, 524 (2)	<10	<10
	UBE2V-43	- (0)	2597, 2477, 402 (3)	244	28,567
	Lck-246	- (0)	>5000, >5000, 227 (3)	196	20,273
GYII-004	SART2-93	- (0)	395, 145 (2)	10	25
	SART3-315	- (0)	785, 144 (2)	11	215
	SART3-109	77 (1)	192 (1)	248	29,511
	Lck-208	- (0)	- (0)	134	19,159

[a]Values of IFN-γ production (pg/ml) in the positive wells are indicated. Number of positive wells in the quadricate cultures is also shown in parenthesis. [b]FIU, fluoresence intensity unit.

indicate that both cellular and humoral responses specific to the vaccinated peptides were truly boosted at the onset of the vaccination-related SAEs. The clinical responses of these 6 patients were 2 PRs and 4 SDs (Table II).

Discussion

In the present study, with the exception of vaccine-related SAEs, the frequencies of SAEs were high in the bladder, pancreas and prostate cancer patients, and low in patients with gastric and colon cancer, or malignant brain tumors. This difference could mainly have been due to the nature of the cancers themselves. The OS of advanced bladder and pancreatic cancer patients at the time of entry to the vaccination trial was very short, ranging from 5 to 8 months, compared to that of patients with advanced gastric and colon cancer (22,23). The exception was prostate cancer, and the OS of advanced prostate cancer patients was relatively long, ranging from 12 to 17 months.

The main reason for the high frequency of SAEs in advanced prostate cancer could be the prolonged vaccination cycles. The median number of vaccinations for advanced prostate cancer patients was 16, with a range of 3 to 112 vaccinations, whereas the median number for patients with other types of advanced cancer was from 6 to 9, as previously reported (4-10,14-25).

Skin reactions at the injection sites were expected, as repeated vaccinations of the peptides along with ISA51 in the subcutaneous regions should elicit inflammatory responses (26), which in turn can result in SAEs in certain cases (4). In addition, anti-tumor responses at the cervical region in cervical cancer patients with a history of radiation therapy and thus are at risk of radiation colitis, could be a risk factor for vaccination-related SAEs.

The number of vaccinations in these 6 cases at the time of SAEs were relatively large, ranging from 7 to 102, as these patients were good responders, suggesting that the vaccination-related SAEs appeared more frequently in patients

who were considered to be good responders. This assumption could be supported by the fact that both cellular and humoral responses specific to the vaccinated peptides, were truly boosted around the onset of the vaccination-related SAEs in all 6 patients.

In conclusion, we show that the majority of SAEs occurring after peptide vaccination for advanced cancer patients were caused by cancer progression. However, it is recommended that physicians should be on guard for vaccine-related SAEs, despite their low incidence.

Acknowledgements

This study was supported in part by a grant from the 'High-Tech Research Center' Project for Private Universities, by matching fund subsidies from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, and by Grants-in-Aid from MEXT. A.Y. and K.I. also received a research grant from Green Peptide Co., Ltd.

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