ORIGINAL ARTICLE

Postoperative DAV-IFN-β therapy does not improve survival rates of stage II and stage III melanoma patients significantly

T. Matsumoto,[1,*] K. Yokota,[1] M. Sawada,[1] A. Sakakibara,[1] S. Shibata,[1] S. Yasue,[1] Y. Tomita,[1] H. Yatsuya,[2,3] M. Akiyama[1]

[1]Department of Dermatology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[2]Department of Public Health and Health Systems, Nagoya University Graduate School of Medicine, Nagoya, Japan
[3]Department of Public Health, Fujita Health University, Toyoake, Japan
*Correspondence: Takaaki Matsumoto. E-mail: tmatsumoto@med.nagoya-u.ac.jp

Abstract

Background DAV-interferon (IFN)-β therapy is a combination chemotherapy of dacarbazine (DTIC), nimustine (ACNU) and vincristine (VCR) with local subcutaneous injection of IFN-β that is widely employed as postoperative adjuvant chemotherapy to treat malignant melanoma in Japan. However, the efficacy of DAV-IFN-β therapy has not been confirmed by randomized controlled trials and the benefit of DAV-IFN-β therapy has not been established yet. This study evaluated the contribution of DAV-IFN-β therapy to improve survival of postoperative patients with cutaneous melanoma.

Methods Patients with stage II or III cutaneous melanoma seen at Nagoya University Hospital from January 1998 to December 2009 were eligible for this study. Disease-free survival rates and melanoma-specific survival rates were evaluated. A propensity score was calculated to control for the effects of variables related to decisions regarding the application of DAV-IFN-β therapy.

Results Eighty-two stage II and 60 stage III melanoma patients were included. In the post-matched stage II patients (17 matched pairs), the mean (±SE) disease-free survival rates were 39.9±13.7% for DAV-IFN-β therapy and 73.1±11.7% for non-use (hazard ratio for recurrence, 2.06; 95% CI, 0.63–6.69; $P = 0.23$), and the melanoma-specific survival rates were 66.2±20.0% for DAV-IFN-β therapy and 86.2±9.1% for non-use (hazard ratio for death, 1.09; 95% CI, 0.17–6.82; $P = 0.93$). In the post-matched stage III patients (nine matched pairs), the disease-free survival rates were 29.6±16.4% for DAV-IFN-β therapy and 33.3±15.7% for non-use (0.69; 95% CI, 0.22–2.17; $P = 0.53$), and the melanoma-specific survival rates were 55.6±16.6% for DAV-IFN-β therapy and 44.4±16.6% for non-use (0.67; 95% CI, 0.18–2.50; $P = 0.55$).

Conclusions DAV-IFN-β therapy brought no significant improvement in either disease-free survival rates or melanoma-specific survival rates of patients with stage II or III cutaneous melanoma. A randomized controlled trial would be required to further evaluate the efficacy of DAV-IFN-β therapy as an adjuvant chemotherapy.

Received: 4 July 2012; Accepted: 16 October 2012

Conflicts of interest

None.

Funding sources

None.

Introduction

DAV-interferon (IFN)-β therapy, a combination chemotherapy of dacarbazine (DTIC), nimustine (ACNU) and vincristine (VCR) in combination with local subcutaneous injection of IFN-β, is widely used to treat malignant melanoma in Japan, especially as postoperative adjuvant chemotherapy. DTIC was first introduced in Japan in 1977, and several combination chemotherapies involving it have been performed since then. DAV combination chemotherapy was reported to improve survival rates of melanoma patients in one multicentre study.[1] Clinical trials of natural IFN-β derived from human fibroblasts, commenced in 1978, revealed an efficacy rate of 50% against cutaneous metastasis of malignant melanoma,[2] and use of IFN-β was supported by another study in 1985.[3] To

further improve the prognosis, the DAV therapy protocol was developed into DAV therapy plus IFN-β, in which DAV is administered in combination with local injection of INF-β (DAV-IFN-β), as a postoperative adjuvant therapy. In 1988, a trial in Japan revealed that the prognosis for malignant melanoma in patients with DAV-IFN-β therapy was better than that for patients with DAV therapy alone, especially among stage III patients.[3] However, the efficacy of DAV-IFN-β therapy has not been established sufficiently, because the above-mentioned studies were not randomized controlled trials, and there seemed to be significant differences in baseline/pretreatment characteristics between the DAV therapy group and the control group, and between DAV-IFN-β therapy groups and patients with simple DAV therapy. Indeed, a randomized trial of adjuvant therapy with DTIC demonstrated no significant effects.[4–6] In the present study, we examined 142 stage II/III cutaneous melanoma patients at our institute to evaluate the contribution of DAV-IFN-β therapy to the improvement of patient prognosis. Propensity score was used to adjust for confounding factors in baseline characteristics.

Patients and methods

Patients

Patients with primary cutaneous melanomas that were classified as stage II or stage III (UICC/AJCC, 2002) seen at Nagoya University Hospital from January 1998 to December 2009 were eligible for this study (142 patients: 82 in stage II; 60 in stage III). All patients underwent wide excision of the primary melanoma, and no patients had chemotherapy or immunotherapy prior to the operation. Except for 17 cases, sentinel lymph node biopsy or lymphadenectomy was performed subsequently or simultaneously. The methods of sentinel lymph node biopsy and pathological evaluation are described elsewhere.[7–11] Patients who had other chemotherapeutic regimens were excluded.

This study was performed according to the principles expressed in the Declaration of Helsinki and the ethics policies of the institution, and was approved by the Ethics Review Committee of Nagoya University Graduate School of Medicine.

DAV-IFN-β protocol and other treatments

As shown in Fig. 1, the DAV-IFN-β therapy recipients were administered DTIC (80–140 mg/m^2, 60-min infusion once a day for five consecutive days), ACNU (50–100 mg/m^2, 30-min infusion on day 1) and VCR (0.5–0.8 mg/m^2, 30-min infusion on day 1) with IFN-β (3×10^6 IU/body, local injection once a day for 10 consecutive days) (Feron®; Toray Industries, Inc., Chuo-ku, Tokyo, Japan). DAV-IFN-β therapy was done every 4 weeks in three cycles for stage II and in five cycles for stage III, in principle. Postoperative maintenance therapy was given to some patients, consisting of local injection of IFN-β. Different from DAV-IFN-β therapy, the main method of this maintenance therapy involves only subcutaneous IFN-β injection around the surgical scar of the primary lesion at a dose of 3×10^6 IU/day every 3–4 weeks for 2–3 years. All patients were monitored postoperatively by means of clinical examinations, blood test and CT or PET/CT at least every 6 months.

Baseline clinical data

Data including those of age, sex, date of first medical examination, site of the primary melanoma, tumour thickness, status of ulceration (with vs. without), treatment history of sentinel lymph node biopsy or lymphadenectomy, status of severe complications (with vs. without) and postoperative performance status (PS) were collected from medical records of the patients at our institute. Regarding tumour thickness and status of ulceration, we excluded cases in which regression was strongly suspected from the present analysis, because tumour thickness did not reflect the disease progression precisely in cases showing regression. Thus, four cases in stage III were excluded from the below-mentioned stratified and matched analysis. Postoperative PS was assessed by the Eastern Cooperative Oncology Group PS scores of 0, 1, 2 and over 2.

For all analyses, patients were divided into two groups: one of DAV-IFN-β therapy use as postoperative adjuvant chemotherapy and the other of non-use.

The primary endpoint among the cohorts was melanoma-specific survival (survival until death from melanoma). The other endpoint was disease-free survival before first recurrence at any site (survival without evidence of recurrence or metastasis). Follow-up and survival periods were calculated from the date of the first medical examination to the date of the last examination or death, until December 2011. Of all the patients, nine patients (four with DAV-IFN-β therapy use and four with non-use in stage II and one with non-use in stage III) were lost between the start of follow-up and December 2011. Survival data or cause and date of death were collected by serial contact with patients and from their medical records.

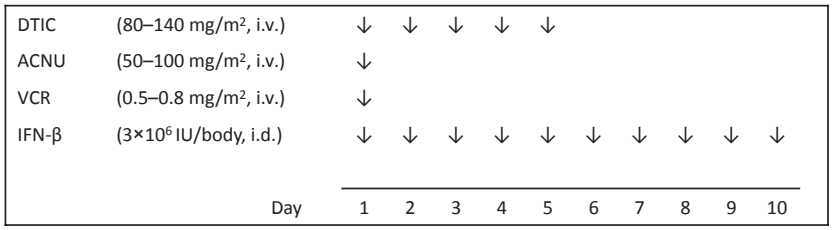

Figure 1 Drug dosage and administration schedule per course of DAV-IFN-β therapy.

Table 1 Baseline characteristics of the patients

	Stage II			Stage III		
	DAV-IFN-β (*N* = 44)	Non-use (*N* = 38)	*P*-value	DAV-IFN-β (*N* = 44)	Non-use (*N* = 16)	*P*-value
Age (years)	60.4 (12.4)	67.3 (16.3)	0.032	58.0 (13.3)	69.3 (10.9)	0.004
Male, *n* (%)	21 (47.7)	18 (47.4)	0.97	24 (54.5)	7 (43.8)	0.46
First medical examination, *n* (%)						
1998–2000	11 (25.0)	3 (7.9)	0.054	8 (18.2)	2 (12.5)	0.90
2001–2003	15 (34.1)	9 (23.7)		9 (20.5)	4 (25.0)	
2004–2006	7 (15.9)	13 (34.2)		16 (36.4)	5 (31.3)	
2007–2009	11 (25.0)	13 (34.2)		11 (25.0)	5 (31.3)	
Primary site, *n* (%)						
Head and neck	6 (13.6)	4 (10.5)	0.182	6 (13.6)	3 (18.8)	0.70
Trunk	4 (9.1)	6 (15.8)		13 (29.5)	5 (31.3)	
Upper extremity	14 (31.8)	5 (13.2)		8 (18.2)	1 (6.3)	
Lower extremity	20 (45.5)	23 (60.5)		17 (38.6)	7 (43.8)	
Tumour thickness (TT; mm)	4.8 (3.1)	5.2 (6.4)	0.81	5.8 (3.8)	7.8 (4.4)	0.13
In situ	0 (0)	0 (0)		0 (0)	0(0)	
TT ≤ 1	0 (0)	0 (0)		1 (2.4)	1 (6.7)	
1 < TT ≤ 2	3 (6.8)	4 (10.5)		5 (12.2)	0 (0)	
2 < TT ≤ 4	24 (54.4)	19 (50.0)		14 (34.1)	2 (13.3)	
4 < TT*	17 (38.6)	15 (39.5)		21 (51.2)	12 (80.0)	
Regression, *n*	0	0		3	1	
Ulceration, *n* (%)	36 (81.8)	26 (68.4)	0.16	26 (63.4)	12 (80.0)	0.24
Regression, *n*	0	0		3	1	
SLNB or lymphadenectomy	39 (88.6)	29 (76.3)	0.14	44 (100)	12 (80.0)	0.002
Severe complication†, *n* (%)	4 (9.1)	17 (44.7)	<0.001	6 (13.6)	7 (46.7)	0.008
Postoperative PS ≥ 2, *n* (%)	4 (9.1)	15 (39.5)	0.001	5 (11.4)	3 (20.0)	0.40
Frequency of DAV-IFN-β	3.25 (1.26)	–	–	3.84 (1.48)	–	–
IFN-β maintenance therapy, *n* (%)	23 (52.3)	26 (68.4)	0.14	25 (56.8)	14 (87.5)	0.028

†Severe complications were defined by following criteria: hepatic complication, serum albumin ≤3.5 g/dl, total bilirubin ≥2.0 mg/dl and/or prolonged prothrombin time (PT); renal complication, glomerular filtration rate (GFR) ≤60% and/or similarity of chronic kidney disease (CKD); respiratory complication, active asthma and/or chronic obstructive pulmonary disease (COPD); cardiovascular complication, New York Heart Association (NYHA) classification class ≥II; and neuropsychiatric complication, dementia that needs fulltime support.
SLNB, sentinel lymph node biopsy; PS, performance status.

Statistical analysis

Continuous variables were expressed as mean (standard deviation) and were compared using the Student's *t*-test. Categorical data were displayed as frequencies and percentages, and were compared using the Chi-squared test. Because patients were not randomly assigned to DAV-IFN-β therapy use or non-use, there were significant differences in baseline covariates between the two groups. Therefore, we used propensity score analyses to control for potential confounding effects of differences in the pretreatment characteristics of DAV-IFN-β therapy use vs. non-use. A propensity score is a measure of the likelihood that a patient will be assigned to DAV-IFN-β therapy or not on the basis of the patient's pretreatment characteristics. To calculate a propensity score for each patient, we estimated the probability that each patient would receive DAV-IFN-β therapy by using logistic regression analysis. Variables included in the logistic model were all the baseline clinical data described above. However, distribution in the variable of sentinel lymph node biopsy or lymphadenectomy was so deflected that we excluded these variables from the model for calculating propensity score. The number of treatment cycles and the presence or absence of postoperative IFN-β maintenance therapy were not included in the multivariate logistic regression analysis because they were post-chemotherapeutic factors and had no effect on decisions regarding DAV-IFN-β therapy. Propensity scores were categorized into four groups by quartiles.

We assessed the relationship between DAV-IFN-β therapy use and study outcome variables by three methods: (i) crude comparison without regard to propensity score; (ii) stratified analysis (crude comparison for each propensity score quartile); and (iii) matched analysis (comparison of survival between propensity score quartile-matched patients with DAV-IFN-β therapy use vs. non-use). For the matched analysis, the number of pairs was

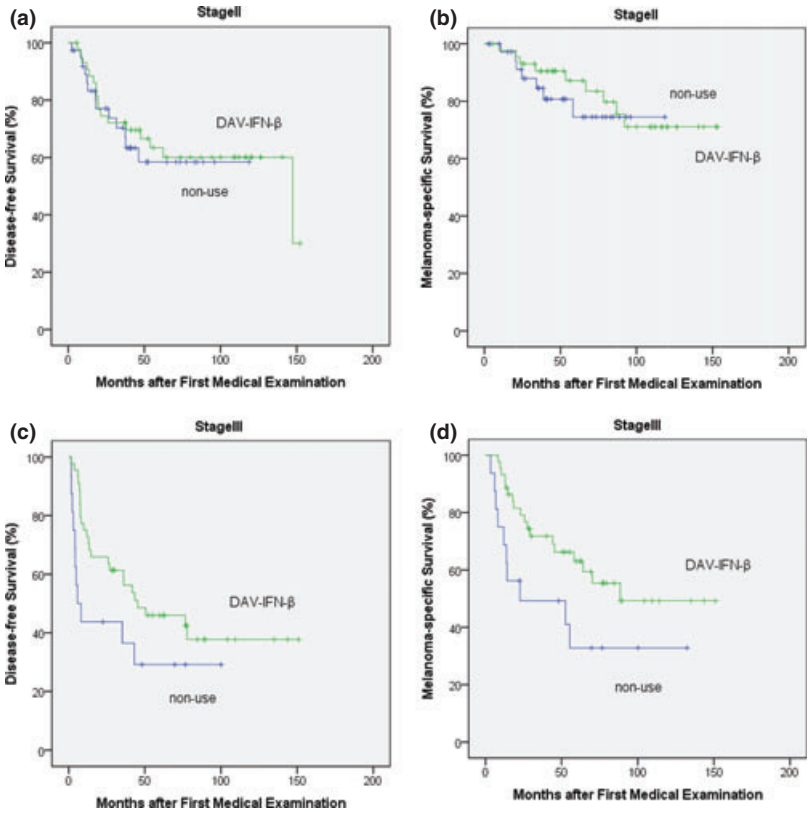

Figure 2 Disease-free survival and melanoma-specific survival in the crude comparison. Disease-free survival (a) and melanoma-specific survival (b) in stage II. Disease-free survival (c) and melanoma-specific survival (d) in stage III. The melanoma-specific survival rate in stage III is higher with DAV-IFN-β therapy use than with non-use, although no significant difference is observed in the disease-free survival rate or the melanoma-specific survival rate either in stage II or stage III. Green dots and lines, patients with DAV-IFN-β therapy; blue dots and lines, patients without DAV-IFN-β therapy.

Table 2 Hazards ratio of DAV-IFN-β therapy

	Pre-match				Post-match	
	Crude		Stratified			
	HR(95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Stage II						
Disease-free	0.87	0.71	1.74	0.37	2.06	0.23
	0.42–1.81		0.52–5.77		0.63–6.69	
Melanoma-specific	0.72	0.53	1.35	0.73	1.09	0.93
	0.26–1.99		0.25–7.27		0.17–6.82	
Stage III						
Disease-free	0.52	0.070	0.55	0.26	0.69	0.53
	0.25–1.06		0.19–1.55		0.22–2.17	
Melanoma-specific	0.47	0.053	0.45	0.21	0.67	0.55
	0.21–1.01		0.13–1.56		0.18–2.50	

HR, hazards ratio; CI, confidence interval.

determined as the number of patients in the smaller of the paired groups (DAV-IFN-β use vs. non-use) for each propensity quartile. Patients in the larger of the two groups (DAV-IFN-β use vs. non-use) were selected randomly for each propensity score quartile.

Kaplan–Meier survival analysis with a log-rank test was used to estimate the mean (±standard error of the mean) disease-free survival rates (no recurrence) and melanoma-specific survival rates (no death from melanoma). For the latter analysis, cases who died from causes other than melanoma were censored at the time of death. In addition, Cox proportional hazard models were also used to estimate the potential benefit of DAV-IFN-β therapy against study outcome variables.

A *P*-value of <0.05 was considered significant. All data were analyzed using SPSS for Windows (SPSS Statistics Version 19; IBM, Armonk, NY, USA).

Table 3 Selection of pair for propensity score matched cohort analysis

Propensity score	DAV-IFN-β	Non-use	Pair selected
Stage II			
0.00086–0.217	0	20	0
0.237–0.561	10	11	10
0.564–0.868	15	6	6
0.910–0.997	19	1	1
Stage III			
0.0077–0.549	4	9	4
0.585–0.899	9	5	5
0.955–0.991	14	0	0
0.992–1.00	14	0	0

Results

Of all the melanoma patients seen at our institute from January 1998 to December 2009, 82 were in stage II and 60 were in stage III. All the studied patients had primary cutaneous melanoma. Patients with mucosal melanoma were not included. During follow-up, 30 (36.6%) stage II and 36 (60.0%) stage III patients had recurrence or metastasis, and 16 (19.5%) stage II and 28 (46.7%) stage III patients died from melanoma. Of all the prematch patients, 44 (53.7%) stage II and 44 (73.3%) stage III patients underwent DAV-IFN-β therapy. In the DAV-IFN-β therapy group, the mean number of treatment cycles was 3.25 (1.26) for stage II and 3.84 (1.48) for stage III. Of the patients who underwent DAV-IFN-β therapy, 23 (52.3%) stage II patients and 25 (56.8%) stage III patients had postoperative IFN-β maintenance therapy (local injection of IFN-β without administration of DAV). The mean follow-up period for all patients was 58.4 (38.9) months. The baseline characteristics of the prematch patients are shown in Table 1.

In the crude comparison, the mean (±SE) estimated disease-free survival rates for stage II were 30.0±21.6% with DAV-IFN-β therapy use and 58.4±9.2% with non-use (hazards ratio for recurrence, 0.87; 95% CI, 0.42–1.81; $P = 0.71$) (Fig. 2a, Table 2). Melanoma-specific survival rates for stage II were 71.1±8.6% with DAV-IFN-β therapy use and 74.5±8.9% with non-use (hazards ratio for death, 0.72; 95% CI, 0.26–1.99; $P = 0.53$) (Fig. 2b, Table 2). Likewise, disease-free survival rates for stage III were 37.8±8.3% with DAV-IFN-β therapy use and 29.2±11.8% with non-use (0.52; 95% CI, 0.25–1.06; $P = 0.070$) (Fig. 2c, Table 2). Melanoma-specific survival rates for stage III were 49.3±9.5% with DAV-IFN-β therapy use and 32.8±12.7% with non-use (0.47; 95% CI, 0.21–1.01; $P = 0.053$) (Fig. 2d, Table 2). Though the disease-free survival rate in each stage was not significantly different, the melanoma-specific survival rate in stage III was close to significantly higher with

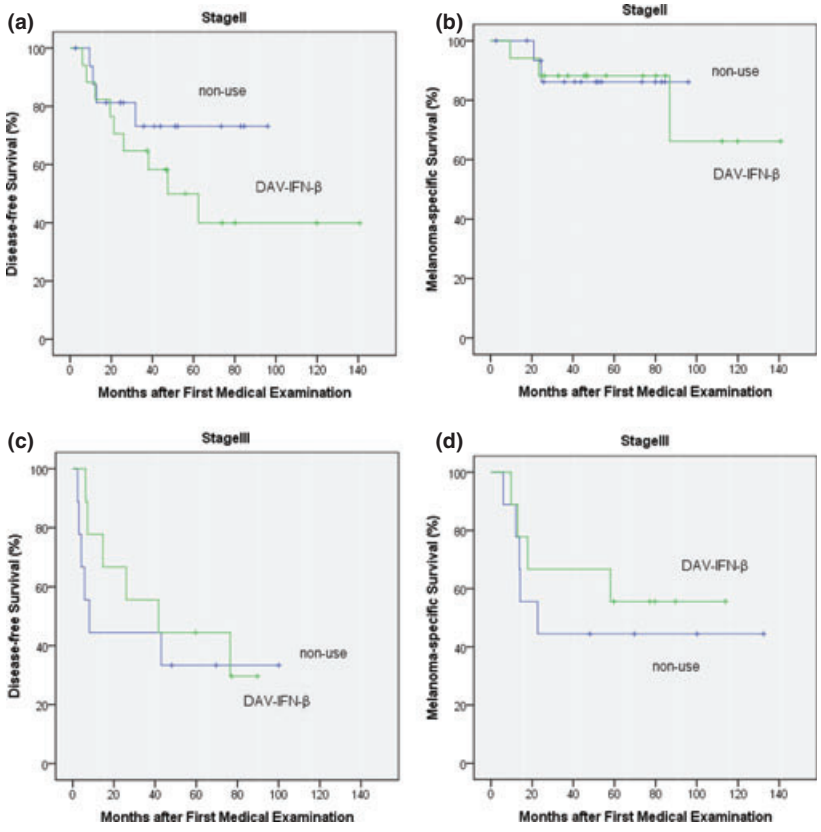

Figure 3 Disease-free survival and melanoma-specific survival in the post-matched patients, using propensity scores. Disease-free survival (a) and melanoma-specific survival (b) in stage II. Disease-free survival (c) and melanoma-specific survival (d) in stage III, respectively. Neither the disease-free survival nor the melanoma-specific survival rate is significantly different between DAV-IFN-β therapy use and non-use in stage II or stage III. Green dots and lines, patients with DAV-IFN-β therapy; blue dots and lines, patients without DAV-IFN-β therapy.

DAV-IFN-β therapy use than with non-use. In the stratified model using propensity scores, no significant difference in survival rates was recognized between DAV-IFN-β therapy use and non-use in either stage II or stage III (hazards ratio for recurrence: 1.74, 95% CI, 0.52–5.77, $P = 0.37$ and 0.55; 95% CI, 0.19–1.55; $P = 0.26$; hazards ratio for death: 1.35, 95% CI, 0.25–7.27; $P = 0.73$ and 0.45, 95% CI, 0.13–1.56; $P = 0.21$, respectively) (Table 2).

Propensity score matching resulted in 17 matched pairs in stage II and nine matched pairs in stage III (Table 3). In the post-matched patients, disease-free survival rates for stage II were 39.9±13.7% with DAV-IFN-β therapy use and 73.1±11.7% with non-use (hazard ratio for recurrence, 2.06; 95% CI, 0.63–6.69; $P = 0.23$) (Fig. 3a, Table 2). Melanoma-specific survival rates for stage II were 66.2±20.0% with DAV-IFN-β therapy use and 86.2±9.1% with non-use (hazard ratio for death, 1.09; 95% CI, 0.17–6.82; $P = 0.93$) (Fig. 3b, Table 2). Likewise, disease-free survival rates for stage III were 29.6±16.4% with DAV-IFN-β therapy use and 33.3±15.7% with non-use (0.69; 95% CI, 0.22–2.17; $P = 0.53$) (Fig. 3c, Table 2). Melanoma-specific survival rates for stage III were 55.6±16.6% with DAV-IFN-β therapy use and 44.4±16.6% with non-use (0.67; 95% CI, 0.18–2.50; $P = 0.55$) (Fig. 3d, Table 2). No significant difference in survival rates was obtained in the patients with DAV-IFN-β therapy use either in stage II or stage III.

Discussion

Chemotherapy is an accepted palliative therapy for stage IV metastatic melanoma,[12–20] and DTIC is the most widely used chemotherapeutic agent for metastatic melanoma.[21] DTIC was originally reported to yield objective responses in up to 25% of patients in older phase II trials, but current large-scale trials with more rigorous criteria have shown response rates of 5–12%.[13,16,17] High-dose IFN-α-2b is the only adjuvant therapy for melanoma approved by the US Food and Drug Administration, although the impact on overall survival is still controversial.[22–25]

The present study was intended to evaluate the contribution of DAV-IFN-β therapy to the improvement of patient prognosis as a postoperative adjuvant chemotherapy. The survival rates of the patients with DAV-IFN-β therapy in the crude comparison at 60-month follow-up were better than those without treatment, similar to the rate of a previously reported study[3] (hazards ratio for death, 0.63; 95% CI, 0.48–0.78, the present study). However, the propensity-score-matched analysis revealed no significant difference between the DAV-IFN-β therapy recipients and non-recipients, either in disease-free survival rates or in melanoma-specific survival rates. Only in the crude comparison for stage III patients, improvement in melanoma-specific survival rates by DAV-IFN-β therapy was almost significant.

This was a single-institute observational study for over a decade. Though propensity score analyses allowed us to replicate some of the characteristics of a randomized controlled trial, they are inherently limited by the number and accuracy of the variables evaluated. In this respect, the numbers of matched pairs in the present study were too small to permit robust conclusions, and we were unable to have an even and a flat population in each stratum that would successfully reduce the deflection between the DAV-IFN-β therapy use group and non-use group. In addition, even after the stratified analysis, other unknown confounders may have affected the outcomes.[26–28]

In conclusion, a propensity-score-matched cohort analysis helps us to reduce bias and gives us a clue to evaluate the efficacy of the therapy. A randomized controlled trial would be required to further define the efficacy and benefit of DAV-IFN-β therapy as a postoperative adjuvant chemotherapy for stage II/III melanoma.

References

1 Ishihara K, Ikeda S, Hirone K *et al.* Prognostic factors for melanoma. *Skin Cancer* 1989; **4**: 349–361.
2 Ishihara K. Clinical research into the use of human fibroblast interferon (Hu IFN-β) to treat malignant skin neoplasia. *J Jpn Soc Cancer Ther* 1983; **18**: 41–53.
3 Yamamoto A, Ishihara K. Clinical study of DAV + IFN-β therapy (combination adjustment therapy with intravenous DTIC, ACNU and VCR, and local injection of IFN-β) for malignant melanoma. *Int J Immunother* 1996; **12**: 73–78.
4 Hill GJ 2nd, Moss SE, Golomb FM *et al.* DTIC and combination therapy for melanoma: III. DTIC (NSC 45388) Surgical Adjuvant Study COG PROTOCOL 7040. *Cancer* 1981; **47**: 2556–2562.
5 Veronesi U, Adamus J, Aubert C *et al.* A randomized trial of adjuvant chemotherapy and immunotherapy in cutaneous melanoma. *N Engl J Med* 1982; **307**: 913–916.
6 Karakousis CP, Emrich LJ. Adjuvant treatment of malignant melanoma with DTIC + estracyt or BCG. *J Surg Oncol* 1987; **36**: 235–238.
7 Morton DL, Wen DR, Wong JH *et al.* Technical details of intraoperative lymphatic mapping for early stage melanoma. *Arch Surg* 1992; **127**: 392–399.
8 Morton DL, Thompson JF, Essner R *et al.* Validation of the accuracy of intraoperative lymphatic mapping and sentinel lymphadenectomy for early-stage melanoma: a multicenter trial. Multicenter Selective Lymphadenectomy Trial Group. *Ann Surg.* 1999; **230**; 453–463; discussion 463–465.
9 Morton DL, Cochran AJ. The case for lymphatic mapping and sentinel lymphadenectomy in the management of primary melanoma. *Br J Dermatol* 2004; **151**: 308–319.
10 Morton DL, Cochran AJ, Thompson JF *et al.* Sentinel node biopsy for early-stage melanoma: accuracy and morbidity in MSLT-I, an international multicenter trial. *Ann Surg.* 2005; **242**; 302–311; discussion 311–313.
11 Matsumoto T, Shibata S, Yasue S *et al.* Interval sentinel lymph nodes in patients with cutaneous melanoma: a single-institution study in Japan. *J Dermatol* 2010; **37**: 629–634.
12 Danson S, Lorigan P, Arance A *et al.* Randomized phase II study of temozolomide given every 8 hours or daily with either interferon alfa-2b or thalidomide in metastatic malignant melanoma. *J Clin Oncol* 2003; **21**: 2551–2557.
13 Avril MF, Aamdal S, Grob JJ *et al.* Fotemustine compared with dacarbazine in patients with disseminated malignant melanoma: a phase III study. *J Clin Oncol* 2004; **22**: 1118–1125.
14 Kaufmann R, Spieth K, Leiter U *et al.* Temozolomide in combination with interferon-alfa versus temozolomide alone in patients with advanced metastatic melanoma: a randomized, phase III, multicenter study from the Dermatologic Cooperative Oncology Group. *J Clin Oncol* 2005; **23**: 9001–9007.

15 Bafaloukos D, Tsoutsos D, Kalofonos H *et al.* Temozolomide and cisplatin versus temozolomide in patients with advanced melanoma: a randomized phase II study of the Hellenic Cooperative Oncology Group. *Ann Oncol* 2005; **16**: 950–957.
16 Bedikian AY, Millward M, Pehamberger H *et al.* Bcl-2 antisense (oblimersen sodium) plus dacarbazine in patients with advanced melanoma: the Oblimersen Melanoma Study Group. *J Clin Oncol* 2006; **24**: 4738–4745.
17 Schadendorf D, Ugurel S, Schuler-Thurner B *et al.* Dacarbazine (DTIC) versus vaccination with autologous peptide-pulsed dendritic cells (DC) in first-line treatment of patients with metastatic melanoma: a randomized phase III trial of the DC study group of the DeCOG. *Ann Oncol* 2006; **17**: 563–570.
18 Middleton M, Hauschild A, Thomson D *et al.* Results of a multicenter randomized study to evaluate the safety and efficacy of combined immunotherapy with interleukin-2, interferon-{alpha}2b and histamine dihydrochloride versus dacarbazine in patients with stage IV melanoma. *Ann Oncol* 2007; **18**: 1691–1697.
19 Ranson M, Hersey P, Thompson D *et al.* Randomized trial of the combination of lomeguatrib and temozolomide compared with temozolomide alone in chemotherapy naive patients with metastatic cutaneous melanoma. *J Clin Oncol* 2007; **25**: 2540–2545.
20 McDermott DF, Sosman JA, Gonzalez R *et al.* Double-blind randomized phase II study of the combination of sorafenib and dacarbazine in patients with advanced melanoma: a report from the 11715 Study Group. *J Clin Oncol* 2008; **26**: 2178–2185.
21 Lens MB, Eisen TG. Systemic chemotherapy in the treatment of malignant melanoma. *Expert Opin Pharmacother* 2003; **4**: 2205–2211.
22 Kirkwood JM, Strawderman MH, Ernstoff MS, Smith TJ, Borden EC, Blum RH. Interferon alfa-2b adjuvant therapy of high-risk resected cutaneous melanoma: the Eastern Cooperative Oncology Group Trial EST 1684. *J Clin Oncol* 1996; **14**: 7–17.
23 Kirkwood JM, Ibrahim JG, Sondak VK *et al.* High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. *J Clin Oncol* 2000; **18**: 2444–2458.
24 Kirkwood JM, Manola J, Ibrahim J, Sondak V, Ernstoff MS, Rao U. A pooled analysis of eastern cooperative oncology group and intergroup trials of adjuvant high-dose interferon for melanoma. *Clin Cancer Res* 2004; **10**: 1670–1677.
25 McMasters KM, Edwards MJ, Ross MI *et al.* Ulceration as a predictive marker for response to adjuvant interferon therapy in melanoma. *Ann Surg*. 2010; **252**; 460–465; discussion 465–466.
26 Balch CM, Gershenwald JE, Soong SJ *et al.* Multivariate analysis of prognostic factors among 2,313 patients with stage III melanoma: comparison of nodal micrometastases versus macrometastases. *J Clin Oncol* 2010; **28**: 2452–2459.
27 Scoggins CR, Bowen AL, Martin RC 2nd *et al.* Prognostic information from sentinel lymph node biopsy in patients with thick melanoma. *Arch Surg* 2010; **145**: 622–627.
28 Murali R, Desilva C, Thompson JF, Scolyer RA. Factors predicting recurrence and survival in sentinel lymph node-positive melanoma patients. *Ann Surg* 2011; **253**: 1155–1164.