Systemic melanoma therapy at the end of life: A single institutional retrospective study in Japan

To the Editor: The treatment of advanced melanoma has drastically changed due to the introduction of novel anticancer agents. However, some caveats remain concerning the excessive drug use in terminal-stage melanoma due to high expectations for their efficacy and tolerability.[1-5] The present study compared the use of anticancer agents in terminal-stage melanoma before and after the introduction of novel agents and identified factors associated with making decisions at the end of life (EOL), especially focused on the final 30 days of life.[1-4]

This retrospective analysis included 69 patients who died of melanoma at Niigata Cancer Center Hospital between 2008 and 2021. We divided the patients into the following 2 categories: the former group ($n = 29$) and the latter group ($n = 40$), before and after the approval of nivolumab, respectively, in July 2014. Between the 2 groups, there were no significant differences in clinical characteristics except for sex ($P = .005$) (Table I). Within 3 months before death, the proportion of patients who received anticancer treatment increased from 17% ($n = 5$) in the former group to 53% ($n = 21$) in the latter group ($P = .005$), and within 30 days before death, it increased from 3% ($n = 1$) to 23% ($n = 9$) ($P = .037$), respectively. In the latter group, the anticancer regimens within 30 days before death consisted of PD-1 inhibitors ($n = 4$), combined nivolumab and ipilimumab ($n = 1$), ipilimumab ($n = 2$), and BRAF/MEK inhibitors ($n = 2$) (Table I). Only 2 of those started first-line treatment within 30 days before death. Six patients had elevated serum LDH (lactate dehydrogenase) levels at the time of the final administration, including 4 who had values more than 2 times the upper limit of normal and 2 who had values more than 10 times.

We analyzed the factors associated with the use of anticancer treatment within 30 days before death in the latter group. There were no significant differences in sex ($P = .98$), age at death ($P = .53$), residence ($P = .77$), or BRAF (v-raf murine sarcoma viral oncogene homolog B1) status ($P = .91$), only in the place of death. Although nearly 70% of patients lived in remote areas relative to our hospital, 78% ($n = 7$) of those who received anticancer treatment died in our hospital, compared to 29% ($n = 9$) of patients who did not ($P < .01$) (Table II).

Table I. Patient characteristics and anticancer treatment in terminal stage

	Former group (2008-2014.7) *n* = 29	Latter group (2014.8-2021) *n* = 40	*P* value*
Characteristics			
Sex			.005
Male	16 (55%)	9 (23%)	
Female	13 (45%)	31 (78%)	
Age at death, y			
Median	65 (37-81)	72 (39-90)	.12
Type			.59
Cutaneous	11 (38%)	21 (53%)	
Acral	13 (45%)	10 (25%)	
Mucosal	2 (7%)	4 (10%)	
N/A	3 (10%)	5 (13%)	
BRAF mutation			N/A
Positive	0 (0%)	10 (25%)	
Negative	0 (0%)	21 (53%)	
N/A	29 (100%)	9 (23%)	
Anticancer treatment in terminal stage			
Within 3 months before death			.005
Use	5 (17%)	21 (53%)	
DTIC-based chemotherapy	5	0	
PD-1 inhibitors	0	10	
Nivolumab + ipilimumab	0	3	
Ipilimumab	0	5	
BRAF/MEK inhibitors	0	3	
No use	24 (83%)	19 (48%)	
Within 30 days before death			.037
Use	1 (3%)	9 (23%)	
DTIC-based chemotherapy	1	0	
PD-1 inhibitors	0	4	
Nivolumab + ipilimumab	0	1	
Ipilimumab	0	2	
BRAF/MEK inhibitors	0	2	
No use	28 (97%)	31 (78%)	

BRAF, v-raf murine sarcoma viral oncogene homolog B1; *MEK*, methyl ethyl ketone; *DTIC*, dacarbazine; *PD-1*, programmed cell death-1; *N/A*, not applicable.
*Chi-square test. $P < .05$ was considered statistically significant.

Table II. Factors associated with anticancer treatment within 30 days before death in the latter group

Characteristics	Anticancer treatment *n* = 9	No anticancer treatment *n* = 31	*P* value*
Sex			.98
Male	2 (22%)	2 (23%)	
Female	7 (78%)	24 (77%)	
Age at death, y			.53
Median	65 (38-86)	74 (34-92)	
Residence			.77
Niigata city†	3 (33%)	12 (39%)	
Other areas	6 (67%)	19 (61%)	
Place of death			<.01
Our hospital	7 (78%)	9 (29%)	
Hometown	2 (22%)	22 (71%)	
BRAF mutation			.91
Positive	2 (22%)	8 (26%)	
Negative	5 (56%)	16 (52%)	
Not applicable	2 (22%)	7 (23%)	

BRAF, v-raf murine sarcoma viral oncogene homolog B1.
*Chi-square test. $P < .05$ was considered statistically significant.
†The city where Niigata Cancer Center Hospital is located.

A retrospective nationwide observational study in the United States showed that the use of ICIs (immune checkpoint inhibitors) for advanced melanoma in the last 30 days of life increased from 16% to 33% after the approval of PD-1 inhibitors.[1] The authors highlighted the need for elevated concern about declining value-based care at the EOL. An Italian multicenter survey showed that death within 30 days after ICI initiation was likely to be observed in patients with a poor performance status and multiple organ metastases.[2] Although there is a limitation in our study because of small sample size, we confirmed that the administration of anticancer agents in terminal-stage melanoma was also increased among Japanese patients. There were some patients who were unable to spend their EOL locally as a result of overtreatment. It may be worthwhile for Asian patients to establish practice guidelines for anticancer treatment in terminal-stage melanoma, though identifying patients unlikely to respond to therapy may require further research.

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Conflicts of interest

TT has received honoraria for lectures from Bristol-Myers Squibb, MSD, Novartis, and Ono Pharmaceutical. The other authors have none to disclose.

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