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Real-world efficacy of nivolumab plus ipilimumab combination therapy versus nivolumab monotherapy for Stage IV melanoma patients in Asia

Recently, the anti-programmed cell death protein 1 (PD-1) inhibitor, nivolumab, and the anti-cytotoxic T-lymphocyte associated protein 4 (CTLA-4) antibody, ipilimumab, have been proven effective in treating Asian melanoma patients [1, 2]. However, group comparisons in clinical trials are lacking, and the superior efficacy of combined anti-PD-1 and anti-CTLA-4 therapy relative to anti-PD-1 monotherapy has not been demonstrated in Asian melanoma studies. We retrospectively analysed the efficacy of nivolumab combined with ipilimumab versus nivolumab monotherapy as first-line treatment. This is the first study reporting the real-world efficacy of these first-line therapies in Asian melanoma patients.

The Ethics Committee of Komagome Hospital (Tokyo, Japan) approved our study per the World Medical Association Declaration of Helsinki. Data on advanced melanoma patients who received first-line nivolumab-based therapy from July 2014 to August 2020, including clinical subtype, serum lactate dehydrogenase level, adverse events (AEs), tumour response, overall survival (OS), and progression-free survival (PFS), were collected. Patients with primary unknown and uveal melanoma were excluded from this study. The first-line therapies used were four cycles of 80 mg nivolumab + 3 mg/kg ipilimumab every three weeks, followed by 240 mg nivolumab every two weeks (combination therapy), and 2 mg/kg nivolumab every three weeks, 3 mg/kg nivolumab every two weeks, or 240 mg nivolumab every two weeks (monotherapy).

Enrolled patients were categorized into combination therapy and monotherapy groups based on the first-line treatment they received. Tumour response was defined according to the Response Evaluation Criteria in Solid Tumours (v. 1.1). AEs were defined according to the Common Terminology Criteria for Adverse Events (v. 5.0). The clinical subtypes of the 75 enrolled patients were as follows: 20 mucosal, 29 non-acral cutaneous and 26 acral lentiginous melanomas (ALMs). Of these, 14 received combination therapy and 61 received monotherapy. The clinical characteristics of enrolled patients are summarized in *table 1*. No statistical difference was observed in baseline patient characteristics between the groups. The response and disease control rates were 43% and 57% in the combination therapy group and 36% and 50% in the monotherapy group, respectively. There was no statistical difference in OS and PFS between the combination therapy and monotherapy groups. The frequency of treatment-related AEs was 71% for all melanoma grades and 36% for Grade 3 or higher in the combination therapy group, and was 48% and 23%, respectively, in the monotherapy group. Nine of the patients in the combination therapy group completed the first four cycles.

Our study revealed no additional survival benefits with combination therapy, moreover, it caused more treatment-related AEs than monotherapy. In previous clinical trials, the efficacy of combination therapies is poorer in Asian studies than in others conducted worldwide. The response rate to nivolumab-based therapy is 43.3% with combination therapy and 34.8% with monotherapy in Asia [1, 2], but 58% and 44%, respectively, in global studies [3]. Only one study in Asia has demonstrated the real-world efficacy of immune checkpoint inhibitors, including non-first-line settings. However, the results of this study revealed no statistical difference in OS between combination therapy and anti-PD-1/anti-CTLA-4 monotherapies, however, combination therapy yielded higher PFS [4]. Regarding the efficacy of ipilimumab-based regimens in Asian patients in clinical practice, one study examined combination therapy and two studies reported on second-line ipilimumab monotherapy, with response rates of only 40.7%, 4.9%, and 3.6%, respectively [5-7]. Based on these results, especially in Asians, ipilimumab may not be as effective as expected in clinical practice, where conditions may be less favourable compared to clinical trials; it may instead cause more AEs. In addition, for ALMs, Rose *et al*. reported no significant survival difference between combined anti-PD-1+anti-CTLA-4 therapy and anti-PD-1 monotherapy [8]. Although the number of cases was small, a similar trend was observed in our study (data not shown). It has also been reported that ALMs account for ∼40% of malignant melanomas in Asia [9] and that melanoma patients with different clinical subtypes tend to have different genetic mutations [10]. Thus, trends observed in Caucasian patients might apply to Asian patients.

Table 1. Clinical characteristics of the enrolled patients.

Group	NI	Nivo	*p*
Sex (female / male)	8 / 6	25 / 36	0.77
Age (mean ± SD)	65.4 ± 16.4	64.3 ± 13.0	0.78
ECOG PS (0 vs 1 vs 2)	10 / 2 / 2	50 / 10 / 1	0.30
LDH (IU/L) ULN (≤ x1 vs x1-2 vs ≥ x2)	7 / 6 / 1	38 / 13 / 10	0.66
BRAF status (positive / negative)	2 / 12	9 / 52	1.00
Subtype			
Acral	5	21	NA
Mucosal	4	16	
Cutaneous	5	24	
M stage			
M1a	2	12	0.27
M1b	5	22	
M1c	1	17	
M1d	6	10	
Metastatic organ (≤ 2 vs ≥ 3)	9 / 5	46 / 15	0.50
RR (%)	42.9	36.1	0.76
DCR (%)	57.1	49.2	0.77
Median OS (months) [95% CI]	NR	20.3 [11.1-29.5]	0.46
Median PFS (months) [95% CI]	3.2 [0.7-5.7]	4.2 [2.3-6.0]	0.99
AEs (%, any grade / ≥ Grade 3)	71 / 36	48 / 23	0.15 / 0.32
Adjuvant treatment			
Nivolumab	2	0	NA
Dabrafenib + trametinib	1	0	
Interferon-β	0	21	
Second-line therapy after treatment failure			
NI	0	6	NA
Ipilimumab	0	11	
Pembrolizumab	1	2	
BRAF/MEK inhibitor	2	5	
Chemotherapy	2	12	
Optimal supportive care	3	18	

NI: combined nivolumab and ipilimumab therapy; Nivo: nivolumab monotherapy; LDH: lactate dehydrogenase; ULN: upper limit of normal; M stage: metastatic stage; RR: response rate; DCR: disease control rate; OS: overall survival; PFS: progression-free survival; NR: not reach; AEs: adverse events; NA: not accessed.

The retrospective nature and small sample size of this study limit the conclusions that may be drawn. Nevertheless, the data from this study and previous studies indicate that the ipilimumab+nivolumab combination may be ineffective in Asian melanoma patients but may increase the risk of treatment-related AEs. Further large-scale studies are needed to confirm these findings. ■

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Squamous cell carcinoma and keratoacanthoma on the neck in a patient with hypohidrotic ectodermal dysplasia

Hypohidrotic ectodermal dysplasia (HED) is a rare hereditary disorder [1]. Most cases exhibit an X-linked recessive inheritance trait (Mendelian Inheritance in Man no. 305100) and are caused by mutations in the ectodyplasin-A (*EDA*) gene [2]. We report a case of HED, which harboured a novel mutation in *EDA* and presented with cutaneous squamous cell carcinoma (SCC).

The patient was a 37-year-old Japanese man with a four-month history of two scaly nodules on his neck. He has never sweated since birth. He experienced atopic dermatitis-like eczema. The two tumours (15×15 mm and 10×10 mm in size) (*figure 1A*) were resected and diagnosed as SCC and keratoacanthoma, respectively (*figure 1B-E*). Positron emission tomography revealed a hot spot on the neck (*figure 1F)*. Biopsies revealed metastatic SCC in the cervical node (*figure 1G)* and dermatitis in the skin with cervical erosive erythema (*figure 1H-I)*. Sweat glands and ducts were absent (*figure 1I)*. Neck dissection was performed. Residual SCC was not found, but slight atypia was observed (*figure 1J*).

We collected a blood sample from the patient, extracted genomic DNA, and performed Sanger sequencing of the *EDA* [2]. Family members were not examined. This study was approved by the Ethics Committee of Niigata University and Yamaguchi University, and adhered to the Declaration of Helsinki Principles. The patient carried a hemizygous splice site mutation c.925-2A>C in intron 7 of the *EDA* gene (*figure 1K*), which was not found in the gnomAD nor the Human Genetic Variation Database. To investigate how the mutation would affect the splicing event, we amplified the sequences containing exons 7 and 8 of the *EDA* by polymerase chain reaction (PCR), and subcloned the products into the pCXN2.1 vector [3]. The vectors were then transfected into HEK293T cells, total RNA was extracted after 24 hours, and reverse-transcription PCR was performed [4]. This *in vitro* transcription assay demonstrated shorter *EDA* cDNA from the mutant (c.925-2A>C) allele, compared to the wild-type allele (*figure 1L*). Sequencing of the shorter product revealed that it lacked a sequence of 32 bp at the 5' end of exon 8 (*figure 1M*), suggesting that the mutation c.925-2A>C destroyed the splice acceptor site of intron 7 leading to aberrant splicing within exon 8 (*figure 1M*). The protein product from this aberrant transcript was predicted to result in a frameshift at codon 309 and an immediate premature termination codon (p.Val309Leufs*2) (*figure 1M*). The truncated protein largely lacks the TNF homology domain of EDA-A1, and this truncation thus most likely abolishes its function.

HED is a hereditary, usually X-linked, disorder with three cardinal features: deficient sweating, sparse hair, and abnormal teeth [1]. Atopic dermatitis-like eczema in HED is thought to be indistinguishable from atopic dermatitis, and it is speculated that hypohidrosis itself might impair the skin barrier [5]. Mutations in *EDA* cause X-linked HED. Although a minority of patients with HED exhibit either an autosomal recessive or dominant inheritance pattern [2,6], genetic analysis confirmed X-linked HED in our case.

Other ectodermal dysplasia syndromes have been associated with malignant tumours. However the association between HED and tumours has only been documented in a few cases [7-10].

The mechanism of carcinogenesis remains unclear, but several possibilities exist. For example, chronic inflammation of severe dermatitis or scratch scar might be associated with cancer. In fact, skin specimens taken from sites near SCC showed carcinoma *in situ* within the epidermis, similar to actinic keratosis without solar damage to the dermis or epidermis. Since our patient mainly worked in the office and remained indoors due to hypohidrosis, his exposure to sunlight was minimal. UV sensitivity tests were not performed. However, he did not experience photodermatosis and was considered too young to have actinic keratosis. As HED is rarely associated with skin cancers, it is unlikely that the *EDA* mutation alone induced the precancerous condition in the epidermis. However, those with atopic dermatitis-like eczema accompanied by HED with injuries acquired by scratching may develop precancerous changes if chronic inflammation is severe. The actinic keratosis-like region may have transformed into SCC.

To the best of our knowledge, this is the first report on HED associated with cervical SCC and keratoacanthoma. We should be vigilant of precancerous skin lesions when managing HED.