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Review

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Treatment strategy after the discontinuation of immunotherapy for head and neck cancer: a review

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Abstract

First-line systemic therapy with immune checkpoint inhibitors (ICIs) is currently the mainstream treatment for recurrent or metastatic squamous cell carcinoma of the head and neck (R/M SCCHN) that is not amenable to local therapy. However, the optimal treatment after discontinuation of ICIs is still unknown, and no large-scale analysis has been conducted in R/M SCCHN. In this narrative review, we summarize the treatment strategies available to continue ICI therapy using the currently available treatment modalities. After the administration of ICIs, unlike cytotoxic agents, the following responses are observed: durable response, pseudo-progressive disease, hyper-progressive disease, mixed response, immune-related adverse events (irAEs), and improved sensitivity to subsequent chemotherapy. Some patients show a durable response to ICIs and a good prognosis; however, many patients will require salvage therapy. We need to select the subsequent treatment according to the various responses unique to ICIs to obtain a durable response. For instance, there are reports on the effectiveness of reapplication of local therapy for a mixed response, retreatment with ICIs, and off-treatment in responsive cases complicated by irAEs. If a durable response can be maintained with ICI therapy, a long-term prognosis that cannot be obtained with conventional chemotherapy can be achieved.

Keywords: Immune checkpoint inhibitors, squamous cell carcinoma, head and neck

INTRODUCTION

Immune checkpoint inhibitors (ICIs) have revolutionized the treatment paradigm for advanced cancers, including recurrent or metastatic head and neck squamous cell cancer (R/M HNSCC). Currently, the programmed death-1 (PD-1) inhibitor pembrolizumab (pembro), used either alone or in combination with platinum/5-fluorouracil (PF) for tumors that express PD-ligand 1 (PD-L1) with a combined positive score (CPS) 1, has replaced combination therapy with chemotherapy and cetuximab as first-line therapy for R/M SCCHN worldwide[1-3]. Moreover, the PD-1 inhibitor nivolumab (NIVO) is one of the most commonly used agents for platinum-refractory disease[4] and is the first choice for platinum-refractory disease in Japan.

Some patients have shown a durable response to ICIs and good prognosis; however, many patients will require sequential treatment with chemotherapy after ICI therapy. The next treatment is selected according to the reasons that led to discontinuation of ICIs and the remaining lesions. However, the optimal treatment after discontinuation of ICIs is still unknown, and no large-scale analysis has been conducted in R/M SCCHN.

The objectives of this study were to investigate the literature related to responses to ICI therapy and treatments after discontinuation of ICI treatment and to summarize the optimal treatment strategy. This is a narrative review of the literature on immunotherapy and salvage treatment concerning R/M SCCHN based on references found in PUBMED, using the following key words: squamous cell carcinoma, recurrent or metastatic, head and neck, immune checkpoint inhibitor, nivolumab, pembrolizumab, salvage chemotherapy, and retreatment.

FIRST-LINE THERAPY WITH ICIS IN R/M HNSCC

Currently, the PD-1 inhibitors pembro and NIVO are used as first-line therapies for R/M SCCHN worldwide. Pembro, with or without chemotherapy, has replaced combination therapy with chemotherapy and cetuximab (EXTREME)[5] as a first-line therapy for R/M SCCHN[1-3]. Pembro alone is used for tumors that express PD-L1 with a CPS 1. However, it should be noted that while the Food and Drug Administration (FDA) approves pembro with chemotherapy regardless of PD-L1 expression, the European Medicines Agency (EMA) only approves it for CPS 1. Patients for whom the pembro regimen is selected as the first-line therapy have R/M SCCHN with platinum-sensitive disease, which includes cases of recurrent or metastatic disease with no history of platinum administration or locally advanced disease that recurred 6 months or later after platinum-containing definitive therapy, and in contrast, patients for whom the NIVO regimen is selected as the first-line therapy have R/M SCCHN with platinum-refractory disease, which includes recurrence occurring within 6 months after platinum-containing definitive therapy[4]. The CheckMate 141 study included the use of NIVO as second-line therapy for patients with disease progression on or after platinum-containing therapy. However, the use of NIVO as second-line therapy is limited in the current era of first-line therapy with pembro. It is currently possible to select ICIs as second-line therapy only in limited cases; for example, after choosing an EXTREME regimen instead of a pembo combination with PF in cases of a CPS < 1, where no prognosis improvement with pembro alone is expected. Such cases met the platinum-refractory category in the CheckMate 141[4] and KEYNOTE-040 studies[6]. Thus, it is important to understand that the current first-line therapy is dominated by the use of two different PD-1 inhibitors, depending on platinum sensitivity.

VARIOUS RESPONSES TO ICIS

Durable response to ICIs

ICIs have been demonstrated to improve overall survival (OS) in many cancer types, including R/M SCCHN. In patients with R/M SCCHN, ICIs have produced a durable response, and long-term survival has

been reported for malignant melanoma[7,8], non-small cell lung carcinoma[9], and renal cell carcinoma[10]. In R/M SCCHN, the 2-year OS rate in the CheckMate 141 study was 16.9%[11], and the 5-year OS rate in a Japanese retrospective observational study was 19.2%[12]. Although there is no standard definition of durable response, a meta-analysis of randomized phase III trials that included at least one ICI arm defined durable response as three times the median progression-free survival (PFS) of the overall population[13]. The durable response was 2.3 times higher in the ICI group than in the control group (25% *vs.* 11%). Furthermore, it was more frequently observed in patients treated with anti-PD-1/PD-L1 antibodies than in those treated with the anti-cytotoxic T-lymphocyte-associated antigen 4 antibody. In cases where a durable response can be obtained, ICIs should be continued with attention to immune-related adverse events (irAEs), as continued ICIs are associated with prolonged survival. However, there is no consensus regarding the duration of ICI treatment. Although there are cases of durable response after discontinuation of ICIs[14], the response to ICIs in patients with progressive disease (PD) after discontinuation of ICIs may have renewed antitumor activity[15]. Therefore, decisions to discontinue ICI treatment outside disease progression or irAEs should be made with caution.

Primary and adaptive resistance to ICIs

Although a certain number of patients showed a durable response in the KEYNOTE-048[1] and CheckMate 141 studies[4], more than half of the patients experienced disease progression in the early stage of ICI treatment. Primary and adaptive resistances to immunotherapy are assumed to be involved in those patients[16]. Unlike cytotoxic agents that act intracellularly, the mechanism of action of ICIs involves the microenvironment surrounding the cancer cells. Resistance to ICIs has been reported to involve the following mechanisms: (1) lack of sufficient or suitable neoantigens; (2) impaired processing or presentation of tumor antigens; (3) impaired intratumoral immune infiltration; (4) impaired interferon gamma signaling; (5) metabolic/inflammatory mediators; (6) immune suppressive cells; (7) alternate immune checkpoints; (8) severe T-cell exhaustion; and (9) T-cell epigenetic changes[17]. The mechanism of resistance to ICIs in head and neck cancer is unknown. However, there have been reports of changes in the therapeutic effect of anticancer agents before and after ICI treatment[18,19] and long-term survival in patients treated with ICIs as second-line therapy after the docetaxel/cisplatin/cetuximab (TPE) and EXTREME regimen as first-line therapy[20], suggesting that changes in the tumor microenvironment around cancer cells due to anticancer agent treatment may alter sensitivity to ICIs. Regardless, the presence of early initial resistance to ICIs must be clearly recognized. In cases of severe symptomatic disease with rapid growth, combination therapy with chemotherapy (pembro + PF) may be preferable over pembro monotherapy in platinum-sensitive disease. In platinum-refractory disease, a regimen such as paclitaxel/cetuximab may be preferable to ICIs in terms of the shrinkage effect of cytotoxic agents.

Pseudo-progressive disease and ICIs

Pseudo-progressive disease (psPD) has been reported in various carcinomas, but its incidence rate is rare, ranging from 1.6% to 9.1%[21]. In a post-hoc analysis of the CheckMate 141 trial, patients were allowed to continue NIVO therapy if their condition permitted it, even if the initial imaging test showed PD. In 15 patients (25%) who continued beyond PD, the tumors subsequently shrank, with a good OS of 12.7 months (95% confidence interval [CI]: 9.7-14.6)[22]. As there were no effective treatments available following immunotherapy at disease progression at the time of the CheckMate 141 trial, continuing immunotherapy beyond PD might have been a viable strategy in anticipation of psPD. However, in the current situation in R/M SCCHN where ICIs are used as the first-line therapy, post-treatment options are available and are expected to be effective; thus, there is little need to anticipate the rare psPD. ICIs may be continued if the patient's quality of life (QOL) is maintained, such as when symptoms improve with ICI treatment, although the tumor is enlarged on imaging. If the disease worsens on imaging and the patient’s symptoms do not improve, it is advisable to move on to the next treatment as soon as possible[23]. The main principle of

treatment for R/M SCCHN is to aim for survival while maintaining the patient's QOL.

Hyper-progressive disease and ICIs

Hyper-progressive disease (HPD) has also been reported in a variety of carcinomas, with incidence rates ranging from 3.8% to 29.4%[22]. Various definitions of HPD have been proposed based on the growth rate before and after ICI administration. In R/M SCCHN, 29.4% of the cases were defined as having double or more tumor growth kinetics[24]. It has the highest number of cases reported among other types of cancer, and it is necessary to pay attention to HPD after the administration of ICIs. Particularly in the head and neck region, rapidly growing lesions tend to be more severely symptomatic and require rapid transition to the next treatment. In first-line therapy with ICIs, it is especially important to consider the possibility of administering second-line treatment. A post-hoc analysis of the KEYNOTE-048 trial showed a prolonged PFS[25]. Since there was no significant difference in PFS in the first-line therapy with pembro *vs*. EXTREME or Pembro + PF *vs*. EXTREME, this result may suggest the efficacy of second-line therapy. However, it is also important to note that there are cases in which second-line therapy has not been administered, and the details have not yet been published.

irAEs by ICIs

When grade 1 irAEs appear according to the Common Terminology Criteria for Adverse Events, version 5.0, ICIs should be continued with careful monitoring, except in cases of some adverse events (AEs), such as transverse myelitis and Guillain-Barré syndrome. In cases of grade 2 irAEs, ICIs should be discontinued, and steroids should be administered according to the grade and type of irAEs. ICIs can be continued in endocrine disorders, e.g., hypopituitarism, hypoadrenocorticism, thyroid dysfunction, hypoparathyroidism, and type 1 diabetes mellitus controlled with hormone replacement. Rechallenge of ICIs should be considered when irAEs have improved to grade 1, and should be based on risk-benefit considerations and in consultation with an organ-specific specialist[26]. In addition, when rechallenging with ICIs, the following points should be considered in determining their adaptation: previous tumor response, duration of treatment, type and severity of the toxicity, time to toxicity resolution, availability of alternate therapies, and patient performance status[27]. The irAEs shown in Table 1 require permanent discontinuation of ICIs according to their grade and type. The grade and type of irAEs require permanent discontinuation changes with each guideline revision, so it is necessary to refer to the latest edition of the guidelines. We might select off-treatment for patients who respond to the initial ICIs and have a durable response, such as a complete response or a good partial response (PR). In cases in which ICIs were discontinued due to irAEs or other reasons not caused by disease progression, there were cases in which a durable response was obtained even after the discontinuation of ICIs, and PFS after the end of treatment was not reached[14]. If a durable response is achieved after ICI cessation, off-treatment is a valid option, given the risk of irAE flare-ups associated with rechallenge with ICIs. In addition, when choosing off-treatment, we need a full explanation of the risk-benefit balance and the patients' understanding under shared decision-making. In this case, the patient should be followed up with careful imaging and medical examinations. When the response is a PR or stable disease to initial ICI treatment but there is a lesion that requires further reduction, rechallenge with ICIs is one of the treatment options. In the case of R/M SCCHN, alternative treatments other than ICIs are possible as the next treatment, and in the case of disease progression, the next treatment should be administered as soon as the irAE status recovers. If the same irAE flares after rechallenge with ICIs, permanent discontinuation is warranted[26].

SUBSEQUENT TREATMENT AFTER INSUFFICIENT ICI THERAPY

Second-line therapy after the discontinuation of ICIs

After discontinuation of first-line therapy with ICIs due to disease progression, it is common to use second-line therapy drugs with a mechanism different from those of the drugs used in first-line therapy. Currently,

Table 1. Type and grade of irAEs requiring permanent discontinuation of immune-checkpoint inhibitors

CTCAE v5.0 grades	Organ	irAEs	
		NCCN guideline[26]	ASCO guideline[27]
All grades	Nervous system	Transverse myelitis Guillain-Barre syndrome	
Grade 2 (Moderate)	Nervous system	Myasthenia gravis	
	Cardio-vascular	Myocarditis	
Grade 3 (Severe)	Hematologic		Hemolytic anemia HUS Acquired hemophilia A
	Nervous system	Peripheral neuropathy Encephalitis	Myasthenia gravis Peripheral neuropathy Autonomic neuropathy Demyelinating disease (including MS, transverse myelitis, ADEM, NMO)
	Ocular		Uveitis/iritis Episcleritis
	Dermatologic	Stevens-Johnson syndrome Toxic epidermal necrolysis	
	Pulmonary	Pneumonitis	Pneumonitis
	Kidney	Proteinuria	Nephritis or AKI
	Musculo-skeletal	Inflammatory arthritis that significantly impairs ADLs and QOL	
Grade 4 (Life-threating)		Acute pancreatitis Diarrhea Colitis Elevated ALT/AST Concomitant elevated bilirubin increases risk of hepatic failure	Bullous dermatoses Severe cutaneous adverse reactions Colitis Infusion-related reaction

CTCAE: Common Terminology Criteria for Adverse Events; NCCN: National Comprehensive Cancer Network; ASCO: American Society of Clinical Oncology; irAE: immune-related adverse event; ADL: activity of daily living; QOL: quality of life; HUS: hemolytic uremic syndrome; MS: multiple sclerosis; ADEM: acute disseminated encephalomyelitis; NMO: neuromyelitis optica; AKI: acute kidney injury.

a regimen combining taxanes and cetuximab appears promising[28]; however, the optimal regimen after ICI treatment is controversial. A phase II/III trial, ECOG-ACRIN EA3202, of chemotherapy + cetuximab *vs.* chemotherapy + bevacizumab *vs.* atezolizumab + bevacizumab following ICI progression in R/M SCCHN (NCT05063552) was conducted. In Japan, five drug classes with different mechanisms of action (platinum agents, ICIs, cetuximab, taxanes, and antimetabolites) are available for head and neck cancers. Agents other than ICIs that have demonstrated prolonged OS should be selected, and if platinum agents are available, combination therapy with platinum and cetuximab should be the first choice. The EXTREME regimen is the first choice after pembro monotherapy as first-line therapy. TPE[20] and paclitaxel/carboplatin/cetuximab regimens[29,30], which are alternative regimens to EXTREME, are also options, considering the patient's condition and outpatient preferences. The paclitaxel/cetuximab regimen is the first choice after pembro + PF or NIVO monotherapy as first-line therapy. Table 2 shows the favorable therapeutic effects of these salvage therapies after ICI discontinuation that have been reported in many cases[28,31-38]. Collectively, previous reports showed an objective response rate (ORR) of 20%-56.5%, disease control rate (DCR) of 47.1%-86.5%, median PFS of 1.0-7.4 months, and median OS of 6.8-15.7 months, which were similar to or better than those after the initial ICI treatment. Although tumors have shrunk, there have been reports of serious complications, such as fistula formation and associated major hemorrhage; therefore, careful administration is necessary[38]. As aforementioned, psPD is a rare reaction, and HPD is reported to be more common in head and neck cancer than in other cancers. Therefore, we believe that subsequent treatment should be initiated promptly at the time of disease progression after the initiation of ICIs. Considering the results of the post-hoc analysis of the KEYNOTE-048 trial[25], it is important to avoid situations in which

Table 2. Summary of the efficacy of salvage chemotherapy after discontinuation of immune-checkpoint inhibitors

References	Number of patients	Regimen of SCT	ORR (%)	DCR (%)	median PFS (months)	Median OS (months)
Wakasaki *et al.*[31]	52	PE (86.5%) PTX (13.5%)	51.9	86.5	7.4	11.9
Wakasaki *et al.*[32]	39	PE (64.1%) S-1 (35.9%)	45.2	85.7	6.5	13.5
Seleh *et al.*[28]	82	Included taxanes (56.1%) Cmab in combination with taxanes or platinum (50.0%) Platinum-based (36.6%)	30	NE	3.6	7.8
Fushimi *et al.*[33]	25	PE (64.0%) EXTREME (16.0%) S-1 (12.0%) PTX (8.0%)	36	NE	2.3	7.3
Pestana *et al.*[34]	43	Anti-EGFR inhibitor (37.2%) Single agent chemotherapy (32.5%) Chemotherapy plus anti-EGFR inhibitor (18.6%) Chemotherapy with other agents (11.6%)	42	NE	4.2	8.4
Kurosaki *et al.*[35]	22	PE (95.5%) S-1 (4.5%)	40.9	86.4	5.2	14.5
Ueki *et al.*[36]	21	PE (61.9%) S-1 (33.3%) PTX (4.8%)	52.4	81	5.4	12.9
Cabezas-Camarero *et al.*[37]	23	PE (73.9%) EXTREME (8.7%) Cisplatin + Cmab (8.7%) Carboplatin + Cmab (8.7%)	56.5	78.3	6.0	12.0
Wakasugi *et al.*[38]*	7	PCE or PE or PTX (85.7%) Others (14.3%)	20	70	1.4	15.7
Wakasugi *et al.*[38]**	16	PCE or PE or PTX (87.5%) Others (12.5%)	23.5	47.1	1.0	6.8

ORR: Objective response rate; DCR: disease control rate; PFS: progression-free survival; OS: overall survival; NE: not estimated; *: cohort with nivolumab after salvage chemotherapy; **: cohort without nivolumab after salvage chemotherapy.

second-line therapy is not available, since sequential treatment until second-line therapy after first-line therapy with ICIs is suggested to prolong OS. The timing of switching to the second-line therapy should be carefully determined because biomarkers that indicate changes in disease progression have not yet been determined. Studies have been conducted using ctDNA[39] and exosomes[40], but with limited results at this time. Meta-analyses[41] have reported that a higher neutrophil-to-lymphocyte ratio is associated with poor OS, PFS, response, and disease control, which may be helpful in conjunction with clinical symptoms and imaging studies.

Mixed response to ICIs

A mixed response is a condition in which the response to ICIs varies from site to site, such as shrinkage of one lesion and enlargement of another[21]. In such cases, the response evaluation criteria in solid tumor evaluation include PD. However, ICI treatment has been successful in shrinking tumor sites, and good results have been reported in patients with R/M SCCHN treated with local treatment for non-responsive sites[38,42,43]. In these cases, a durable response was achieved by retreatment with ICIs after local treatment. Regarding radiotherapy (RT) as a local treatment, there have been reports of the abscopal effect, a phenomenon in which lesions in areas distant from the irradiated site shrink, and there have been some reports of R/M SCCHN[38,44]. This is thought to be the result of RT-induced changes in the immune cell type within the tumor cells, activation of dendritic cells caused by cancer antigen release from tumor cells, and activation and proliferation of tumor antigen-specific T cells[45,46]. Generally, when local therapy is not

indicated for recurrent or metastatic disease, systemic therapy, including ICIs, is the treatment of choice. However, when mixed responses are observed, the option of local treatment of progressive lesions with a tumor microenvironment that does not respond to ICIs may be considered in terms of a strategy to achieve a durable response. Thus, local treatment in the recurrent or metastatic setting is considered one of the treatments that should be reconsidered for long-term continuation of ICI treatment. Regarding local treatment, surgery and RT have been reported so far; however, treatments such as near-infrared photoimmunotherapy (NIR-PIT) and boron neutron capture therapy (BNCT) are also promising options for R/M SCCHN. NIR-PIT involves the intravenous injection of antibody-photosensitizer conjugate (APC), followed by illumination of the tumor with NIR light (690 nm), which kills only APC-bound target cells[47]. The delivery of NIR light to the target tissue is very crucial, and tumors that cannot be irradiated with NIR light (for example, tumors with vascular invasion) are difficult to treat. BNCT is a type of particle beam radiation therapy that utilizes an alpha particle and 7Li nucleus generated when a thermal neutron is captured by a 10B nucleus that has selectively taken up the boron compound in tumor tissue[48]. These treatments are available for inoperable and previously irradiated R/M SCCHN, and might be effective in selected cases but require further investigation.

Retreatment with ICIs

Systemic therapy is selected for R/M SCCHN when there is no indication for local treatment. In systemic therapy, drugs that have been used once and have failed should not be readministered in subsequent treatment. Depending on the patients' response to ICIs, local treatment and attempts to retreat with ICIs have been reported. A systematic review of four studies evaluating retreatment with a PD-1 inhibitor revealed an ORR of 23%-36%, a DCR of 40%-64%, a median OS of 13.4-20.6 months, and a rate of AEs above grade 3 of < 10%[49]. The cancer types retreated with ICIs are malignant melanoma and non-small cell lung cancer, and the previous review did not include head and neck cancer. We reported 12 cases of retreatment with NIVO in R/M SCCHN[38]. In Japan, retreatment with pembrolizumab is not covered by insurance, but retreatment with NIVO is allowed in patients who have received platinum agents; therefore, NIVO was administered to all patients. Patients who had undergone some form of salvage treatment after the discontinuation of the initial ICI treatment were divided into two groups: those who were retreated with NIVO (Niv cohort) and those who were not (No Niv cohort). A comparison of OS from the start of salvage treatment after the discontinuation of ICI showed a significant difference (P = 0.034) in the survival of 5.8 months (95%CI: 2.4-9.2) in the No Niv cohort compared to 17.5 months (95%CI: 2.7-32.3) in the Niv cohort. Only retreatment with NIVO significantly reduced the risk of death in both univariate and multivariate analyses of salvage treatment after discontinuation of ICI treatment. In the Niv cohort, NIVO was readministered after disease control with RT or salvage chemotherapy. The differences between the Niv and No Niv cohorts were in PFS and OS for the initial ICI treatment, both of which were significantly prolonged in the Niv cohort. In other words, it has been suggested that after disease progression of the initial ICI and salvage treatment with RT or chemotherapy, ICIs may be readministered to provide long-term survival in patients who respond to initial ICI treatment. In second-line therapy, it was stated that drugs with a mechanism that has been used once should not be readministered, but the effect of the ICIs depends on the tumor microenvironment, and the immune environment may change with the addition of some treatment. Therefore, the option of readministration may be considered with respect to ICIs, but further studies are needed on this topic.

Overview of the treatment strategy

Figure 1 shows an overview of the treatment strategy after the discontinuation of ICI treatment. ICIs are the current standard first-line therapy for R/M SCCHN. ICI treatment is expected to lead to a long-term prognosis in patients with a durable response. Although there are cases in which a durable response can be obtained with initial ICI treatment, many patients will require discontinuation of ICI treatment due to

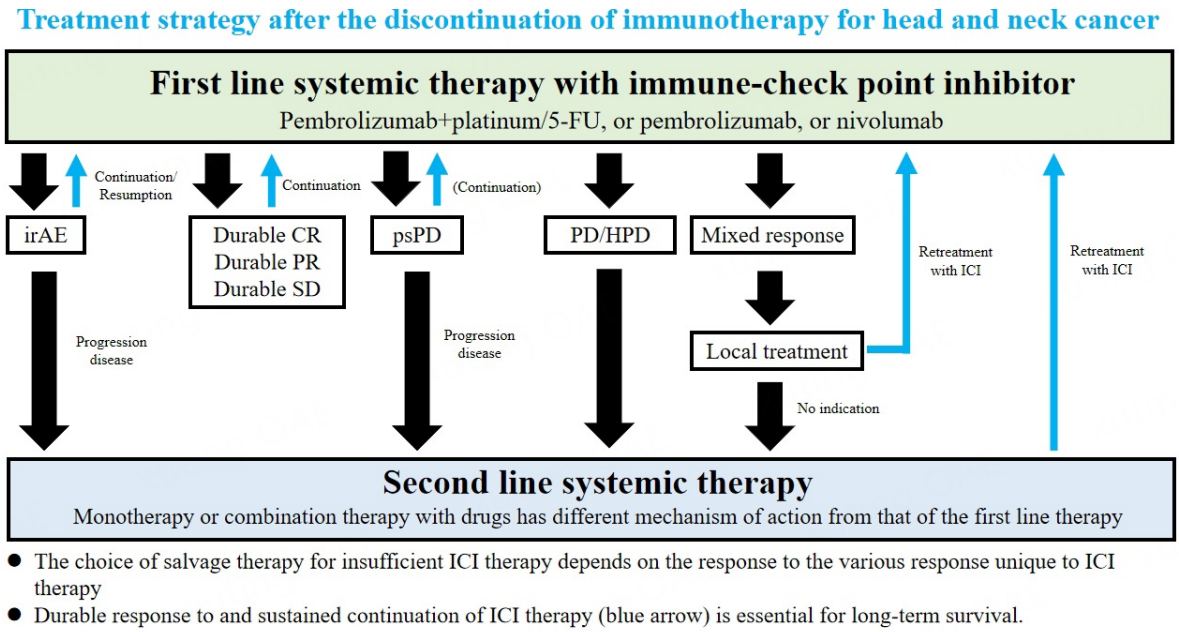

Figure 1. Overview of first-line therapy with immune-check point inhibitor and subsequent treatment. Figure created by the author. irAE: Immune-related adverse event, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, psPD: pseudo-progressive disease, HPD: hyper-progressive disease, ICI: immune-checkpoint inhibitor.

irAEs, PD, HPD, and a mixed response. In such cases, it is important to select treatments according to the various responses associated with ICI treatment, and sometimes local treatment, such as RT or surgery, is used to shrink the tumor and achieve a durable response. In some cases, ICIs were withdrawn due to the appearance of irAEs, but sustained shrinkage was observed. In these cases, careful judgment is required regarding the resumption of ICIs, depending on the type of irAEs. In first-line systemic therapy with ICIs, it is important to switch to second-line systemic therapy at the appropriate time if the observed disease progression is unsuitable for continued ICI or local treatment. In general, if ICI treatment is unsuccessful, it should not be rechallenged. However, some cases have achieved long-term survival through retreatment with NIVO after achieving a durable response through non-ICI therapy.

CONCLUSIONS

In first-line systemic therapy with ICIs in R/M SCCHN, it is important to note that a variety of reactions can occur after the administration of ICIs. The choice of salvage therapy for insufficient ICI therapy depends on the unique response of the patient to ICI therapy, and local therapy might be effective in addition to second-line systemic therapy. Durable response to and sustained continuation of ICI therapy are essential for long-term survival. For this purpose, the option of retreatment with ICIs might be promising after a durable response is obtained with salvage therapy. However, the limitation of treatment strategies after discontinuation of ICIs in head and neck cancer is that only retrospective studies in a limited number of patients have been reported. Further investigation is needed.

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The author contributed solely to the article.

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