short review

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Current systemic treatment options and new developments in palliative first-line treatment of head and neck squamous cell carcinoma

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Summary This short review gives an overview of current treatment concepts, recently published trials, and novel developments in relapsed or metastatic head and neck squamous cell carcinoma (HNSCC) not amendable for local curative treatment. Trials with potential future clinical implications and relevant updates of landmark trials are provided as well.

Keywords Head and neck squamous cell carcinoma (HNSCC) · Palliative first-line tratment · Recent trials · Treatment algorithm

Introduction

In recent years different clinical trials have been published that have substantially altered the first-line treatment landscape in patients with relapsed or metastatic head and neck squamous cell carcinoma (HNSCC). This short review provides a condensed overview on studies relevant for first-line treatment and gives on outlook on promising treatment options.

Recent studies in the first-line palliative treatment setting

The anti-programmed cell death protein 1 (PD1) antibody pembrolizumab with or without platinum/5-FU is considered as the standard treatment approach in patients with relapsed or metastatic HNSCC with a PD-L1 combined positive score (CPS) ≥ 1 [1] who are not amendable for local curative treatment concepts. This recommendation is based on the results of the KEYNOTE-048 study showing that pembrolizumab +/− chemotherapy improves overall survival (OS) compared to the EXTREME-regimen (Platinum/5-FU/cetuximab) in the prespecified subgroups with a PD-L1 CPS ≥ 1 and ≥ 20, respectively [2]. Recently, an update of this trial revealed an ongoing benefit of the pembrolizumab containing regimens compared to EXTREME: in the CPS ≥ 1 population, 5-year OS was 15.4% for pembrolizumab monotherapy, and 18.2% for pembrolizumab + chemotherapy. In the CPS ≥ 20 subgroup a slightly higher 5-year OS for pembrolizumab and pembrolizumab + chemotherapy of 19.9% and 23.9% was reported [3].

Results from large phase III trials comparing anti-PD-(L)1 and anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibodies with the EXTREME regimen were recently published. In the CheckMate 651 trial nivolumab plus ipilimumab versus the EXTREME regimen was evaluated [4]. Primary endpoint of the study was OS in the CPS ≥ 20 subcohort (38.3% of the study population). The study failed to meet its primary endpoint. In the CPS ≥ 20 subgroup median OS for nivolumab/ipilimumab and EXTREME were 17.6 months and 14.6 months (HR 0.78, 95% CI 0.59–1.03, $p = 0.0496$), respectively. Comparable observations were made in the KESTREL study [5]. In this open-label three arm trial patients were randomized to durvalumab, durvalumab/tremelimumab or the EXTREME regimen. The primary objective of the study was OS of durvalumab monotherapy compared to EXTREME in patients with high PD-L1 expression (defined as PD-L1 expression on tumor cells ≥ 50% or immune cells ≥ 25%). Durvalumab was not superior compared to EXTREME in PD-L1 high expressors (durvalumab vs. EXTREME median OS 10.9 months vs. 10.9 months, HR 0.96, 95% CI 0.69–1.32). Moreover, the addition of tremelimumab to durvalumab

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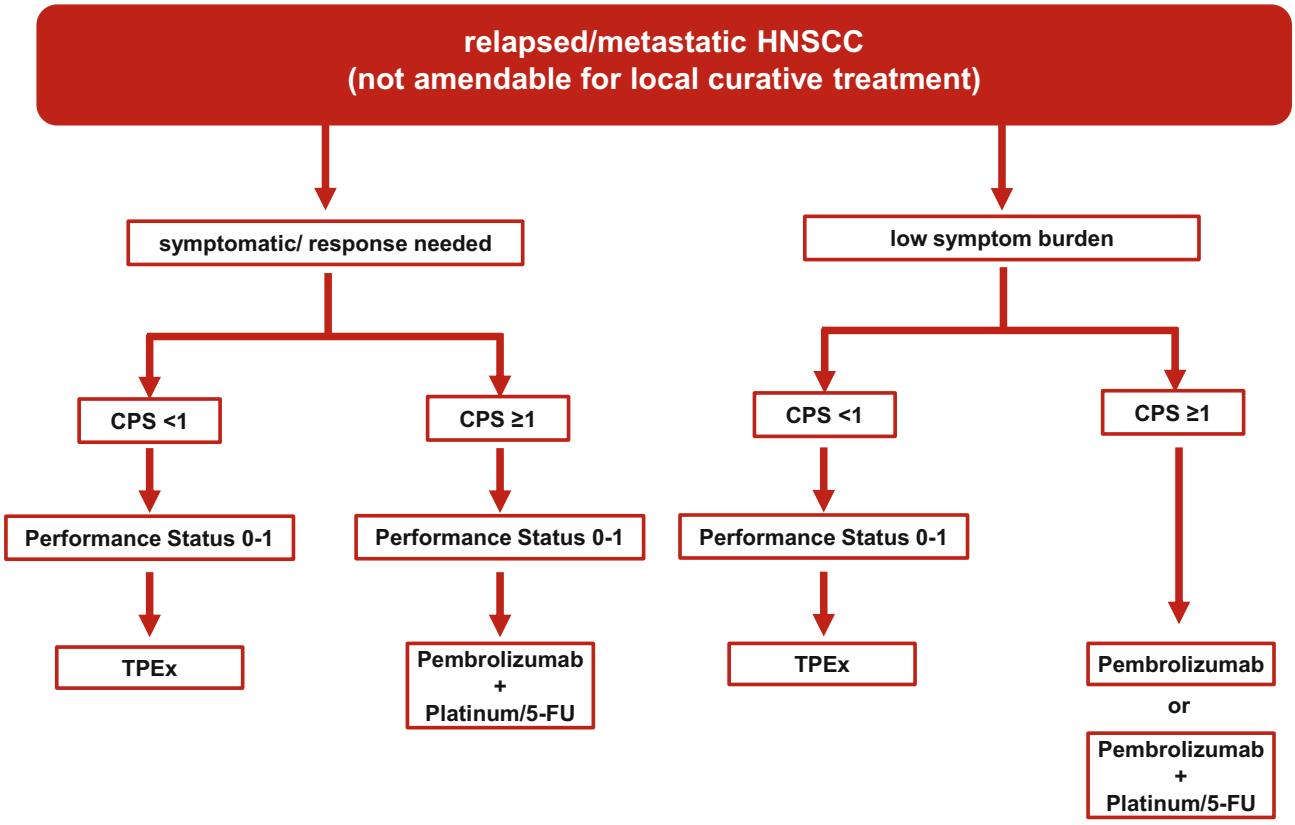

Fig. 1 Treatment algorithm for relapsed/metastatic HNSCC patients not amendable to local curative treatment

did not result in better OS compared to EXTREME (durvalumab/tremelimumab median OS 11.2 mo, HR 1.05, 95% CI 0.80–1.39) in the PD-L1 high cohort.

Besides platinum, continuous 5-fluorouracil (5-FU) over 4 days is a long-standing part of the first-line chemotherapy backbone [6]. However, 5-FU is associated with an increased risk of toxicity especially in patients with dihydropyrimidine dehydrogenase (DPD) deficiency that is present in approximately 3–5% of the general population [7, 8]. Consequently, the European Medical Agency recommends DPD testing prior to treatment with 5-FU [9]. The combination of cisplatin/paclitaxel showed similar efficacy compared to cisplatin/5-FU in an early phase III trial [10]. Recently, first results of the phase IV KEYNOTE B-10 trial, investigating carboplatin/paclitaxel + pembrolizumab, were presented. In this open-label, single arm, study an ORR of 42.7% was reported [11]. Interestingly, response seemed to be irrespective to the PD-L1 CPS expression. However, this finding should be interpreted cautiously due to the small number of included patients ($n = 92$).

Further strategies to improve outcome in the first-line setting include combinational approaches of checkpoint inhibitors with tyrosine kinase inhibitors (TKIs): According to a phase II single arm study the combination of cabozantinib and pembrolizumab resulted in an ORR of 52% and a clinical benefit rate of 91% [12]. No association of response with PD-L1 CPS was observed. The reported median PFS of 14.6 months seems encouraging in the light of other trials investigating checkpoint inhibitors in HNSCC. Lenvatinib plus pembrolizumab was investigated in a phase IB/II trial [13]. ORR in the 22 included patients with HNSCC was 46%. For this reason, the clinical phase III LEAP-010 study (NCT04199104) was initiated to elaborate the efficacy of lenvatinib plus pembrolizumab seen in the early phase study.

In an open-label phase II multi-arm trial the efficacy of pembrolizumab in combination with the anti-EGFR antibody cetuximab is evaluated in different treatment settings [14]. First results of cohort 1 (patients without previous PD-(L)1 or EGFR inhibition) have been reported. This combination yielded a promising ORR of 45% and a median PFS of 6.5 months.

In PD-L1 negative patients (i.e. CPS < 1), or contraindications for checkpoint-inhibitor treatment, cetuximab-based regimens are still the preferred options [1]. In the phase III EXTREME trial the addition of cetuximab to platinum/5-FU resulted in an OS improvement (HR 0.80; 95% CI 0.64–0.99; $p = 0.04$) [6]. In the randomized TPExtreme trial four cycles of the taxane-containing TPEx regimen (cetuximab/cisplatin/docetaxel) were compared to 6 cycles of the EXTREME regimen [15]. Chemotherapy was followed by cetuximab maintenance in both arms. Even though the TPExtreme trial failed to meet the primary endpoint of

OS improvement (HR 0.89. 95% CI 0.74–1.08, $p = 0.23$), this regimen was not inferior to the EXTREME arm and was associated with a favourable safety profile including substantially lower rates of neutropenia (24% vs. 49%), haemoglobin decrease (8% vs. 20%) and thrombopenia (2% vs. 20%). Figure 1 provides a proposed treatment algorithm in the first line setting.

Discussion

In the relapsed and metastatic setting, treatment with pembrolizumab +/− chemotherapy represents the standard of care in patients with PD-L1 CPS ≥1. A recent update of the KEYNOTE-048 trial revealed an ongoing long-term benefit compared to the EXTREME regimen. Nevertheless, it has to be mentioned that ORR for pembrolizumab monotherapy was inferior with 19.1% and 23.2% in the CPS ≥1 and CPS ≥20 subgroups compared to EXTREME (ORR 34.9% and 36.1%). On the other hand, ORR was comparable for pembrolizumab + chemotherapy (CPS ≥1: 36.4%; CPS ≥20: 42.9%). A recent post-hoc analysis of the KEYNOTE-048 study indicated only modest activity of pembrolizumab monotherapy in the subcohort of patients with CPS <1 (ORR: 4.5%, median PFS: 2.1 months, median OS: 7.9 months) [16]. In the CPS 1–19 subcohort, pembrolizumab monotherapy yielded a comparable 12-month OS with 44% compared to the EXTREME–standard arm (42%; HR 0.86 95% CI 0.66–1.12). Up to now, further analyses on different CPS cut-offs are lacking (i.e. CPS >50). Two phase III studies have investigated the checkpoint inhibitor combination of PD-(L)1 and CTLA-4 antibodies in HNSCC patients with a high PD-L1 expression. Neither in the KESTREL study (tremelimumab/durvalumab) nor in the Checkmate 651 study (ipilimumab/nivolumab) a survival benefit was observed when comparing with the EXTREME regimen. Thus, based on current evidence, the combination of chemotherapy and pembrolizumab might be the favoured option in rapidly progressing or highly symptomatic HNSCC patients harbouring a CPS ≥1 to induce response and prolong PFS.

Encouraging results have been reported in single-arm trials evaluating checkpoint inhibitors with TKIs. Despite signs of clinical activity, randomized studies are required to proof these novel treatment concepts. Another, yet to be answered question, is if the addition of a TKI or antibody has the potential to re-induce responses in patients progressing upon checkpoint inhibitors. Results regarding pembrolizumab plus cetuximab in the EGFR- or checkpoint inhibitor-refractory setting are still pending. Of note, a phase III trial that investigated monalizumab, a checkpoint inhibitor targeting NKG2A, in combination with cetuximab, in checkpoint inhibitor pretreated patients was stopped early due to lack of efficacy (NCT04590963).

First results of the KEYNOTE-B10 study indicate that an alternative chemotherapy backbone might be a rational option in patients harbouring DPD deficiency. Up to now, OS data is still immature. Nevertheless, this study represents another proof that taxane-containing treatment is efficacious in the first-line setting. In this context comparable observations were made in the TPExtreme trial: for the TPEx arm an ORR of 46% was reported. Despite the fact that this trial failed to reach the primary endpoint of OS superiority, several findings are in favour of the TPEx regimen compared to EXTREME including: a shorter duration of the chemotherapy administration (1 day vs. 4 days), lower number of chemotherapy cycles (4 vs. 6 cycles), favourable toxicity profile (adverse events ≥4°: 36% vs. 51%), comparable median PFS (6.0 months vs. 6.2 months) and median OS (14.5 months vs 13.4 months).

Conclusion

Currently, first-line palliative treatment selection in patients with HNSCC is primarily based on PD-L1 CPS expression. While in patients with CPS ≥1 pembrolizumab +/− chemotherapy has evolved as the preferred regimen, cetuximab-based treatment is still the favoured option in case of a CPS <1. Negative results of phase III trials investigating anti-PD-(L)1 + anti-CTLA-4 antibody combinations in PD-L1 preselected cohorts might be considered as a hint that chemotherapy still has its role even in PD-L1 high expressors. Alternative taxane-based chemotherapy backbones have exaggerated the treatment armamentarium and are characterized by encouraging response rates. Especially the KEYNOTE B-10 regimen might be considered as the preferred option in patients with DPD-deficiency. Novel combinations of checkpoint inhibitors with TKIs show encouraging clinical activity as well. However, phase III trials are needed to proof their effectiveness.

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Conflict of interest F. Kocher and A. Seeber declare that they have no competing interests.

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