Chapter 13
Is there a Role for Neoadjuvant Targeted Therapy and Immunotherapy?

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Abbreviations

^{18}FDG-PET	18- fluorodeoxyglucose-positron emission tomography
EGFR	Epidermal growth factor receptor
G-CSF	Granulocyte-colony stimulating factor
PD(−L)	Programmed death (-Ligand)
SAE	Severe adverse events
SCCHN	Squamous cell carcinoma of the head and neck
SUV	Standardized uptake value
TPF	Taxanes, platinum-based chemotherapy and 5-fluorouracil

Introduction

The role of induction or neoadjuvant therapy to treat locally advanced squamous cell carcinoma of the head and neck (SCCHN) is controversial [1, 2]. Standard treatment remains concomitant chemoradiation with high-dose (100 mg/m^2) cisplatin when a non-surgical approach is preferred [1, 2]. The only recognized indication for induction chemotherapy is larynx preservation, and the oncological outcome is similar to that of concomitant chemoradiation in this particular setting [3]. Taxane/platinum/5-Fluorouracil (TPF) combinations have proven to be superior to

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platinum/5-fluorouracil schedules, and TPF is therefore now the accepted standard for induction [4, 5].

In this chapter, we review if there is a role forneoadjuvant targeted therapy or immunotherapy in the treatment of SCCHN. We discuss two different approaches: neoadjuvant or induction studies and window of opportunity trials.

Induction Therapy with Targeted Therapy and Immune Checkpoint Inhibitors

In a neoadjuvant or induction approach, the definitive standard treatment (i.e. surgery or (chemo)radiation) is delayed to allow enough time for the neoadjuvant agent(s) to produce a therapeutic response and improve overall treatment efficacy. In this setting, the use of drugs targeting the epidermal growth factor receptor (EGFR) has been largely investigated in combination with chemotherapy.

Three trials have studied the safety and feasibility of combining cetuximab with TPF [6–8]. Specenier et al. investigated four cycles of TPF plus cetuximab (TPF-E) (cisplatin and docetaxel 75 mg/m^2 on day 1 followed by 5-fluoruracil (5-FU) 750 mg/m^2/day as a continuous infusion on days 1–5 plus cetuximab at a loading dose of 400 mg/m^2 followed by a weekly dose of 250 mg/m^2), with prophylactic antibiotics but no growth factors [6]. Induction TPF-E was discontinued in 13% of patients due to toxicity, and three out of 46 patients developed a bowel perforation. Only 65% of the patients in this study started chemoradiation. Mesia et al., using the same TPF regimen but with prophylactic granulocyte-colony stimulating factor (G-CSF) and antibiotics, observed febrile neutropenia, grade III/IV diarrhea and toxic death in 24%, 20% and 6% of patients, respectively [7]. It was therefore deemed that TPF-E leads to unacceptable toxicities. In contrast, Haddad et al. found that it was feasible to give three cycles of TPF-E with cisplatin 100 mg/m^2 day 1, docetaxel 75 mg/m^2 day 1 and 5-FU 850 mg/m^2/day as a continuous infusion on days 1–4 plus cetuximab for a total of six weeks given on days 1 and 8 of each cycle of TPF [8]. Similarly, a phase I trial combined lapatinib with TPF, but this combination also resulted in prohibitive toxicities [9].

Therefore, several single arm phase II trials evaluated the combination of cetuximab with a platinum compound and a taxane but without 5-FU [10–14]. In most of the trials, these combinations were found to be feasible, and observed objective response rates of between 70% and 97% were promising (Table 13.1).

A small number of randomized trials have compared cetuximab/platinum/taxane-based induction chemotherapy versus TP(F) [15–17]. No clinically significant differences were observed between the cetuximab-based regimens and the controls (Table 13.2). Therefore, the role of induction therapy with a targeted agent to treat SCCHN remains purely investigational.

Table 13.1 Single arm phase II trials investigating cetuximab with a platinum compound and a taxane

Regimens	N	ORR	3-year PFS rate	3-year OS
Cisplatin + Docetaxel + Cetuximab [10]	39	86%	70%	74%
Cisplatin + Docetaxel + Cetuximab [11]	54	72.2%	58.2%	90.7%
Carboplatin (AUC2) + Paclitaxel (135 mg/m2/ weeks) + Cetuximab [12]	47	96%	87%	91%
Carboplatin (AUC2) + Paclitaxel (90mg/m2/weeks) + Cetuximab [13]	30	97%	NA	NA
Carboplatin (AUC2) + Paclitaxel (90 mg/m2/ weeks) + Cetuximab [14]	63	70%	55%	78%

NA not-available; *AUC* area under the curve: *ORR* objective response rate; *PFS* progression-free survival; *OS* overall survival; *y* year

Table 13.2 Randomized phase II trials investigating cetuximab with a platinum compound and a taxane

Regimens	N	ORR	3-year PFS rate	3-year OS
Cisplatin + Docetaxel	44	82%	56%	74%
Versus				
Cisplatin + Docetaxel + Cetuximab [15]	48	81%	70%	88%
Regimens	N	ORR	400-day PFS rate	400-day OS rate
Cisplatin + Docetaxel +5-fluorouracil	50	77%	67%	86%
Versus				
Cisplatin + Docetaxel + Cetuximab [16]	50	86%	70%	79%
Regimens	N	ORR	2-year LFS rate	2-year OS rate
Cisplatin + Docetaxel + (5-fluorouracil)	180	82%	46%	68%
Versus				
Cisplatin + Docetaxel + (5-Fluorouracil) + Cetuximab [17]		81%	47%	69%

NA not-available; *AUC* area under the curve: *ORR* objective response rate; *PFS* progression-free survival; *LFS* laryngectomy-free survival: *OS* overall survival; *y*:year

Based on the promising efficacy of some window trials, immune checkpoint inhibitors are also under evaluation. A phase III trial is currently investigating the standard of care versus two cycles of neoadjuvant pembrolizumab (200 mg every 3 weeks) followed by curative-intent surgery and postoperative pembrolizumab-based (chemo)radiation [18]. One of the primary endpoints is pathological response after neoadjuvant therapy (<10% of tumor cells within the resected primary tumor and lymph nodes). The study design is depicted in Fig. 13.1.

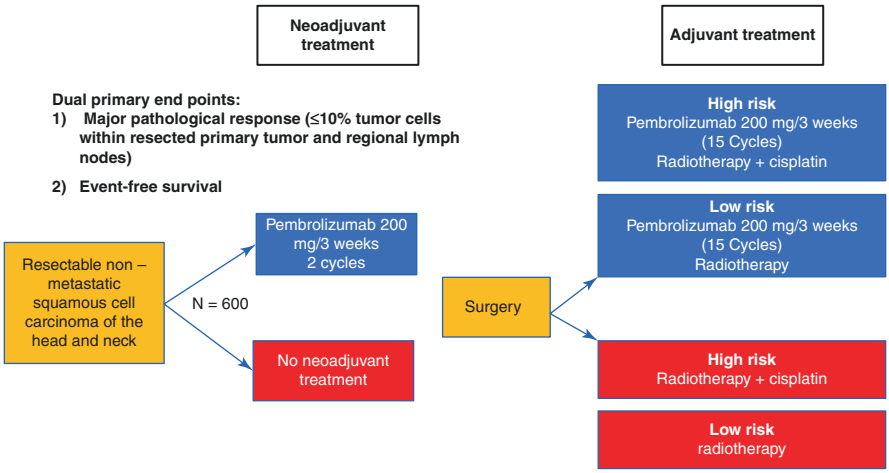

Fig. 13.1 KEYNOTE-689: Phase III study of adjuvant and neoadjuvant pembrolizumab combined with standard of care in patients with resectable, locally advanced head and neck squamous cell carcinoma

Window of Opportunity Trials with Targeted Therapy and Immune Checkpoint Inhibitors

Window of opportunity studies are trials in which patients receive one new compound in the period between their cancer diagnosis and the start of standard therapy. The primary objective of this approach is not treatment efficacy but translational research. Standard treatment is usually surgery. Tumor biopsies and anatomic and functional imaging are performed before and after investigational treatment for translational research (Fig. 13.2). The main advantage of this study design is the ability to investigate new molecules in patients who have not yet been treated by multiple anti-cancer therapies. Traditionally, drugs are often tested in patients with locoregional or metastatic recurrence whose tumors are predominantly resistant and there is a risk that the activity of these agents may be underestimated. Furthermore, the understanding of the biological and molecular effects of these tested drugs may be limited in palliative patients because it could be perceived unethical to perform additional biopsies for research purposes only. In head and neck cancer window studies, pretreatment biopsies during diagnostic endoscopy and post-treatment biopsies on the day of surgery can be performed, taking advantage of general anesthesia. The evaluation of new compounds using this approach prior to classical curative treatment provides information about molecular and clinical activity as well as predictive biomarkers [19, 20].

Window of opportunity studies aim to maximize the information gain whilst minimizing the risk to patients who are awaiting potentially curative treatment. Standard treatment should therefore not be delayed due to the investigational drugs' study procedures or side effects. Some studies have shown that curative treatment in head and neck cancer should be carried out within 20 to 28 days after diagnosis [21, 22],

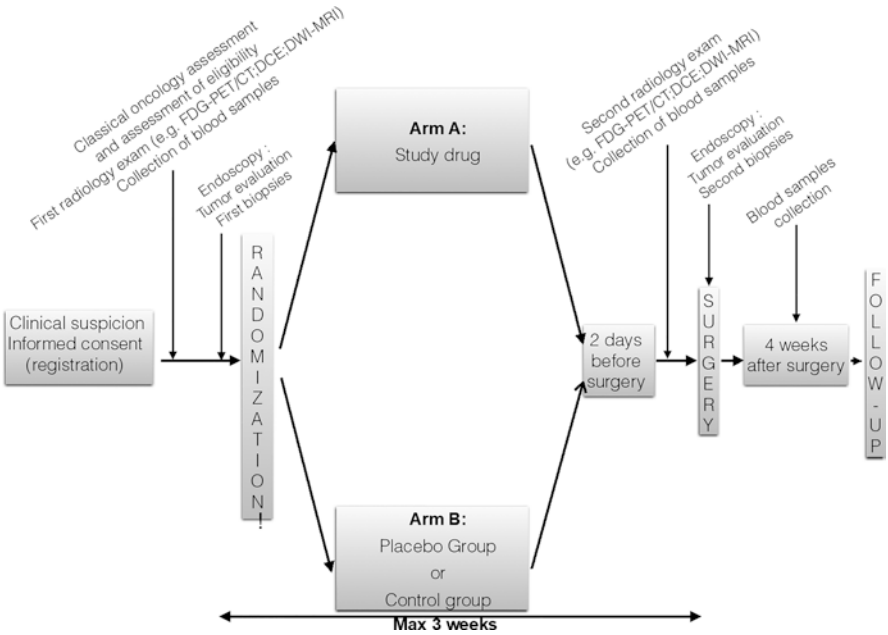

Fig. 13.2 Example of a window of opportunity study design. *FDG-PET* fluorodeoxyglucose-positron emission tomography; *DCE* dynamic contrast enhanced; *DWI-MRI diffusion*-weighted magnetic resonance imaging

making trial organization one of the main challenges for this type of study. To achieve this goal, we recommend that patients with SCCHN be included in window studies at the time of clinical diagnosis, that the time points for biopsies and imaging are prospectively pre-defined, and that the schedule, dose, and duration of the preoperative treatment are standardized and the same for all patients. Finally, to validate translational research, patients should also be randomized against a control/placebo group. If macroscopic tumor reduction is observed with the investigational compound, surgery should be performed as initially planned to ensure that the extracted surgical specimen has clear margins without microscopic tumor invasion.

Several PD1/PD-L1 monoclonal antibodies and anti-EGFR agents have been investigated in this setting (Tables 13.3 and 13.4). Interestingly, and aside from molecular activity, clinical efficacy has sometimes been detected even if the treatment period was short (<4 weeks). We will discuss some examples to highlight the advantages and drawbacks of this research approach.

Schmitz et al. [21, 23, 24] investigated cetuximab versus controls in the two weeks before curative surgery in treatment-naïve patients with SCCHN. The primary endpoint of safety was reached with cetuximab prior to surgery. Cetuximab also induced a high rate of response based on 18-fluorodeoxyglucose-positron emission tomography (^{18}FDG-PET) evaluation and a decrease in tumor cellularity, which significantly correlated with ^{18}FDG-PET response. Four patients out of 20 also had a

Table 13.3 Window of opportunity studies with targeted therapies in SCCHN (non-exhaustive list)

Trial	N	Clinical compound	Control arm	Primary end point	Severe toxicities (i.e. grade 4)	Trial duration	Delay in surgery
Thomas [28] (2007)	35	Erlotinib	None	Tumor size and immunohistochemistry	0%	18–30 days	No
Del Campo [29] 2011)	107	Lapatinib	Placebo group (n = 36)	Apoptotic index	0%	2–6 weeks	NA
Schmitz [21] (2014)	33	Cetuximab	Control group (n = 5)	Safety and 18FDG-PET response	3% (first part) 0% (second part)	2 weeks**	No
Gross [30] (2014)	49	1. Erlotinib 2. Erlotinib +Sulindac	Placebo group (n = 12)	Ki67 modulation	0%	2 weeks	No information
Brana [31] (2014)	14	Dacomitinib	Placebo group (randomisation 2:1)	Evaluation of a genes expression signature	No information	7–11 days	No information
Bauman [32] (2014)	58	1. Erlotinib 2. Desatinib 3. Erlotinib +Desatinib	Placebo group (randomisation 1:1:1:1)	Percent change in RECIST-measurable index lesions	0%	7–21 days	No information
Machiels [25] (2018)	30	Afatinib	Control group (n = 5)	Metabolic 18FDG-PET response	0%	2 weeks	Yes (for 3 patients)
Nair [33] (2019)	64	1. Erlotinib 2. Celocoxib 3. Erlotinib +Celocoxib	Control group (n = 16)	Tumor response (clinical and MRI)	0%	21 days	No information

* Window study before curative (chemo)radiotherapy

** in the second part of the trial

NA not available; *18FDG-PET* 18-fluorodeoxyglucose-positron emission tomography; *MRI* magnetic resonance imaging

Table 13.4 Window of opportunity studies with immunotherapy and other therapies in SCCHN (non-exhaustive list)

Trial	N	Clinical compound	Control arm	Primary end point	Severe toxicities (i.e grade 4)	Trial duration	Delay in surgery
Ferris [26] (2017)	29	Nivolumab	None	Safety	0%	29 (± 7) days	No
Horton [34] (2019)	9	Nivolumab	None	Overall Response rate	0%	2 weeks	No
Uppaluri [35] (study still ongoing: NCT02296684)	21*	1. Pembrolizumab during preoperative period 2. Pembrolizumab during preoperative period + one year of Pembrolizumab during postoperative period	None	1-year Locoregionnal Recurrence	0%	2–3 weeks for the preoperative part of the trial	No
Curry [36] (2017)	50	Metformine	None	Immunohistochemistry for metabolic markers	0%	9 -24 days	No information
Berinstein [37] (2018)	27	IRX-2	None	Modulation of Lymphocyte Infiltration	0%	21 days	No
Miles B and Sikora A (study still ongoing: NCT02002182)	±30	ADXS11–001	Control group	Change in HPV E6/E7-specific CD8+ cytotoxic lymphocyte (CTL) responses in the peripheral blood and safety	No information	33 days	No information

* According to the abstract of ASCO 2017

macroscopic reduction in the size of their tumor. Gene expression analyses showed that in some patients cetuximab increased the expression of genes involved in epithelial to mesenchymal transition and activation of cancer-associated fibroblasts.

Afatinib, an irreversible pan-ErbB inhibitor, has also been investigated in a multicenter randomized window study of 25 treated patients versus five controls [25]. The primary endpoint was ^{18}FDG-PET response. Seventy percent of the patients showed a partial metabolic response and 22% of patients had a partial response according to RECIST v1.1. A high cluster 3-hypoxia score and wild *TP53* status were predictive of treatment activity. The investigational compound was considered safe even though three patients experienced surgical delay. Among them, two delays (3 and 24 days, respectively) were related to drug toxicity. We therefore believe that it is preferable to use drugs that have already proven to be safe in phase I studies in order to maximize patient safety and to protect the initiation of standard treatment. To the best of our knowledge, very few window studies in head and neck oncology have had to deal with grade ≥ 4 or unexpected side effects.

In 2017, Ferris et al. [26] conducted a window study with nivolumab, a monoclonal antibody targeting PD-1, in 29 SCCHN patients. Patients received two doses prior to surgery that was planned on day 29 ± 7. The primary endpoint was safety. The publication is still pending, but according to the ESMO 2017 abstract, grade 3–4 treatment-related adverse events occurred in four patients without delaying surgery. Tumor shrinkage, assessed by computer tomography (CT)-scan just before surgery, was observed in 48% of evaluable patients. Three patients experienced tumor reduction ≥40% (largest reduction = 75%). However, 11 patients also showed an increase in tumor size (the largest by 100%). At this stage, it is not possible to differentiate between true tumor progression or pseudo-progression.

More recently, vaccine-based therapies have begun to be investigated using window study designs. The main challenge for vaccines using this trial design is the limited period of time that short-term vaccination has available to show effective immunological effects. In this context, we recommend the use of minimally invasive samples (e.g. blood tests) to investigate the therapeutic effect of these vaccines after standard curative treatment, for example four weeks after surgery, as shown in Fig. 13.2. A meta-analysis of 239 phase I therapeutic cancer vaccine trials, conducted by Rahma et al. [27], concluded that the risk of severe adverse events (SAEs) when testing therapeutic cancer vaccines is extremely low and that AEs did not correlate with dose levels. Several window studies investigating the use of short-term therapeutic vaccination in head and neck cancers are currently in progress. First results are pending.

Conclusion

Targeted and immune therapies as induction or neoadjuvant therapy are not standard of care and should be reserved for clinical trials. In this context, a phase III trial is investigating neoadjuvant and adjuvant pembrolizumab in patients selected for a primary surgical treatment. Window of opportunity trials are important translational research tools that require careful design and an experienced team.

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