Optimal treatment for recurrent/metastatic head and neck cancer

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While a large proportion of patients presenting with stage I and II squamous cell carcinoma of the head and neck (SCCHN) will remain disease free after single modality treatment, the majority of patients presenting in a more advanced disease stage and very often treated with a form of combined modality treatment, will eventually relapse, either locoregionally only, at distant sites only or both. A few patients with a locoregional recurrence can be salvaged by surgery or reirradiation. However, most patients with recurrent or metastatic (R/M) disease only qualify for palliative treatment. Treatment options in these patients include supportive care only, or in addition single agent chemotherapy, combination chemotherapy or targeted therapies either alone or in combination with cytotoxic agents. Prognostic factors analysis in such patients treated with (platinum-based) chemotherapy has identified five adverse prognostic factors, which seems worthwhile to take into consideration when performing trials; one pathologic feature (tumor cell differentiation) and four clinical baseline characteristics (ECOG performance status, weight loss, location of the primary tumor and prior radiotherapy). Moreover, it has been shown that response to systemic therapy has a major impact on survival. None of the trials performed in the past, even those with a reasonable sample size, have shown that aggressive platinum-based combination chemotherapy leads to survival benefit when compared to single agent methotrexate, cisplatin or 5-fluorouracil. After decades without real progress, a recent European randomized trial showed that adding cetuximab, the first clinically available EGFR-directed monoclonal antibody, to a standard chemotherapy regimen (platinum/5-fluorouracil) leads to an important survival benefit and this, with support of an additional smaller study in the US, has changed practice.

introduction

Squamous cell carcinoma of the head and neck (SCCHN) is considered to be the final stage of a multi-step process evolving from normal histology to hyperplasia, mild dysplasia, moderate dysplasia, severe dysplasia, carcinoma in situ, to invasive carcinoma. Particular chromosomal alterations appear to be associated with distinct stages of tumor progression [1]. Underlying genetic instabilities including the loss of heterozygocity (LOH) of certain chromosomes (3p14, 9p21, 17p13, 8p, 11q, 13q, 14q, 6p, 4q27 and 10q23) and amplification, deletion, up-regulation or down-regulation of certain oncogenes or tumor-suppressor genes, including epidermal growth factor receptor (EGFR), p53, Rb, p65, cyclooxygenase 2 (COX-2), p16, cyclin D1 and phosphatase and tensin homolog (PTEN) have been identified as genetic alterations in each of the pathological stages of this disease [1].

Head and neck cancer is the sixth most common cancer worldwide [2] and there has been a significant increase in the global incidence of SCCHN over the past decade [3]. At present, >650 000 new cases of head and neck cancer are diagnosed each year worldwide [4, 5]. In Europe alone, it is estimated that there are ~143 000 new cases and >68 000 deaths due to the disease each year [5].

The management of SCCHN is complex and requires a multidisciplinary approach involving medical oncologists, radiation oncologists, head and neck surgeons, radiologists, speech therapists, social workers, psychologists, plastic and/or reconstructive surgeons, dentists with particular interest and expertise in head and neck cancer [6, 7].

Single-modality treatment with surgery or radiotherapy is generally recommended for the ~40% of patients who present with stage I or II disease. Each of the two modalities results in similar survival with cure rates ranging between 60% and 90% depending on tumor site and extension of the disease. The choice between the treatment modalities depends on tumor site, extension of the disease, patient preference, comorbidities, expertise of the multidisciplinary team, available equipment, etc. Salvage with the alternative treatment modality is frequently possible in cases of local relapse after the primary treatment. Over the years, significant advances in surgical and radiation techniques have reduced the toxic effects without compromising the outcome.

For the 60% of the patients who present with locally advanced disease at diagnosis, combined modality therapy is generally recommended. For patients with unresectable disease the current standard treatment is concurrent cisplatin-based
chemoradiation. This is also the standard for patients with resectable disease when organ preservation is desired and, as adjuvant treatment, for patients with high-risk pathological findings at surgical resection. Despite such an approach, the majority of patients develop local and/or regional recurrences and distant metastases occur in 20%–30% of patients [4, 6–10]. A few patients with a locoregional recurrence can be salvaged by surgery or re-irradiation. However, most patients with recurrent or metastatic (R/M) disease only qualify for palliative treatment. Treatment options in these patients include supportive care only, or in addition single-agent chemotherapy, combination chemotherapy or targeted therapies either alone or in combination with cytotoxic agents. Treatment choice should be based on factors such as performance status (PS), co-morbidity, prior treatment, symptoms, patient preference and logistics [9]. Goals of treatments in these circumstances are mainly symptom control and prevention of new cancer-related symptoms, improvement in quality of life (QoL) and if assessable, objective tumor response (OR), disease stabilization (SD) or both combined (disease control; DC) and in addition prolongation of overall survival (OS) and progression-free survival (PFS). Unfortunately, correlation between objective tumor reduction (or DC) and subjective benefit (symptom control and QoL) has not been adequately studied, underscoring the importance of clinical trials in this patient group [10].

Patients with R/M-SCCHN can have specific problems related to their social habits such as ongoing heavy tobacco and alcohol use or the use of other carcinogens, which may lead to poor cognitive function, co-morbidity medical conditions (cardiovascular and/or pulmonary diseases) and malnutrition. Moreover, typically disease-related problems may be present, such as infections (local, aspiration pneumonia, systemic), hypercalcemia, local pain or bleeding (arterial, venous, capillary), which can all influence QoL and OS and may necessitate active supportive care [11].

prognostic factors
patients undergoing re-irradiation

Prognosis is poor when a recurrence or new primary head and neck cancer develops in an area previously treated with radiation [12]. In the absence of disease at distant sites, salvage surgery may provide a durable DC in ~15% of such patients [13]. However, in those with positive surgical margins, or adverse pathologic features the outcome is still expected to be poor after salvage surgery. For the many patients with unresectable disease at the time of recurrence, the disease was uniformly fatal, and only palliative treatment options, as described above, were left and for some this meant the use of platinum-based chemotherapy, providing a typical median survival of 6 months [9].

However, in recent years the practice of full-dose re-irradiation has come forward as an option and literature data indicate that with the use of re-irradiation durable DC in ~10% of patients with unresected tumors and in 20% of those with resected tumors can be obtained [14, 15]. Because considerable toxicity might go along with this approach, Tanvetyanon et al. [12], in a retrospective study, tried to define which patients might benefit from re-irradiation and who most likely will not. They reviewed the medical records of 103 patients who had undergone radiation between January 1998 and 2008 and in whom there had been significant overlap of re-irradiation field and the previously irradiated area. They studied potential prognostic factors, including co-morbidity and pre-existing organ dysfunction, for survival after re-irradiation. In this study, co-morbidity was assessed by Charlson index and Adult Comorbidity Evaluation-27 (ACE-27) grading and organ dysfunction was defined as feeding tube dependency, functioning tracheostomy or soft tissue defect including uncovered open wound of skin or mucosa, fistula or osteonecrosis. Approximately 70% of patients had also received chemotherapy concurrent with radiation. In the multivariate analysis, co-morbidity (by either Charlson index or ACE-27), radiation dose, organ dysfunction, recurrent tumor stage, tumor bulk at re-irradiation and time interval between previous radiation and re-irradiation were all independent prognostic factors. Median OS was 5.5 months among those with both organ dysfunction and co-morbidity per Charlson index, and 4.9 months per ACE-27, compared with 59.6 and 44.2 months, respectively, among the patients with neither organ dysfunction nor co-morbidity (P < 0.001 and P < 0.001).

patients receiving chemotherapy

Prognostic factors and characteristics of long-term survivors in R/M-SCCHN patients treated with platinum-based combination chemotherapy regimens were identified from an analysis of two Eastern Cooperative Oncology Group (ECOG) randomized trials (E1395 and E1393) [16]. The median follow-up of the patients in these two trials was 4.7 years; survival rates at 1, 2, 3 and 5 years were 32%, 12%, 7% and 3.6%, respectively and median OS was 7.8 months. The OR rate was 32%. On multivariate analysis, the investigators were able to identify one pathologic feature (tumor cell differentiation) and four clinical baseline characteristics (ECOG PS, weight loss, location of the primary tumor and prior radiotherapy) as independent predictors of OS. They constructed a prognostic model for OS based on the presence of these five independent prognostic factors and were able to categorize the patients into two groups with significantly different outcome, i.e. one in which patients had only two or fewer adverse prognostic factors and another in which patients had three or more poor prognostic factors. The first group had a median survival that was nearly twice that of the second group (0.98 years compared with 0.52 years). They also identified that the same variables and the presence of residual tumor at the primary site were independent predictors of response to chemotherapy. In fact, response to chemotherapy was found to be of prognostic significance. When the investigators added response to chemotherapy to the model, the location of the primary tumor lost its prognostic significance but all other parameters, including tumor cell differentiation, retained their significance as independent predictors of survival. Predictors of 2-year survivorship were response to chemotherapy (complete or partial response versus no response), white race (versus others), ECOG PS of 0 (versus 1), poor cell differentiation (versus well/moderate) and no prior radiotherapy. Interestingly, all long-term survivors had
locally recurrent disease at study entry. The take-home messages from this analysis are that (i) response to systemic therapy has a major impact on survival, (ii) patients with locally recurrent disease, but not the patients with distant metastases, who are primarily treated with chemotherapy, will rarely be cured of their disease, and (iii) future trials in patients with R/M-SCCHN should take the five adverse prognostic factors into consideration.

It is therefore clear that for any definitive conclusion on the superiority of one treatment over another, cross-trial comparisons are rather misleading and may lead to incorrect conclusions as result of variations in tumor and patient characteristics. Illustrative of this are the favorable data in some of the non-randomized trials with new cytotoxic agents and the negative randomized trials when these same agents are compared in a randomized trial versus standard methotrexate (see below). This is also true both for the first-line and second-line settings. For making a fair judgement on its value, a new drug should be tested in a direct comparison against a standard treatment or a placebo or tested as an adjunct to standard therapy versus standard therapy alone.

**systemic treatment**

**single-agent chemotherapy**

A large number of conventional single agents have been investigated in the past in patients with R/M-SCCHN [11, 14]. The four most active and most extensively used agents are methotrexate, cisplatin, 5-fluorouracil (5-FU) and bleomycin. These drugs produced a response of short duration, ~3–5 months, in 15%–30% of cases and only rarely complete response (CR). Several new active agents (defined as inducing responses in ≥15% of cases) have been introduced more recently, such as pemetrexed, vinorelbine, irinotecan, capecitabine, orzel, S-1 and the taxanes paclitaxel and docetaxel [10, 17–22]. The taxanes are among the highest scoring agents, with response rates varying between 20% and 43%, illustrating the earlier mentioned variability in patient and tumor characteristics. For most of the conventional agents, but also of the newer agents, no direct comparison has been made with the standard palliative agent methotrexate. There are a few exceptions to this unfortunate situation, i.e. there have been direct comparisons with methotrexate for the methotrexate analog edetrexate [23], the platinum compound cisplatin [24, 25] and the taxanes [26, 27]. Apart from the phase III trial on edetrexate versus methotrexate, none of the other studies was large enough to allow for a survival comparison, but there was no indication of any superiority. Nevertheless, in the randomized phase II study of docetaxel versus methotrexate [27], the response rate was reported as significantly higher in the docetaxel arm with 27% [95% confidence interval (CI) 21.7% to 32.3%] OR compared with 15% [95% CI 11.2% to 18.8%] in the methotrexate arm. Whether this increased activity of docetaxel in the R/M disease setting has significance for treatment outcome will need to be explored in a phase III trial.

It is currently unclear whether any of the cytotoxic agents prolongs survival when compared with supportive care alone as an adequately powered randomized controlled trial has never been performed. Only one small study in the past was designed to demonstrate clinical benefit over best supportive care (BSC) only, using randomized controlled trial methodology. In that trial, 31 patients treated with single-agent cisplatin demonstrated prolonged survival compared with 26 patients treated with supportive measures only [28]. An interesting aspect of this trial was the demonstration that patients who respond do so quickly. Of the 16 responders, 75% responded after the first cycle and the remaining 25% after the second cycle [10].

**combination chemotherapy**

*standard platinum-based combinations.* Combination chemotherapy is very often considered in younger patients with a good performance, in particular when favorable prognostic factors for response to chemotherapy are available [11]. The Wayne State University cisplatin/infusional 5-FU (PF) regimen gradually emerged as the most commonly used combination chemotherapy regimen in patients with SCCHN. With that regimen, non-randomized trials indicated a better outcome than what was observed with single-agent treatment, at least with respect to OR rates and CR rates [29]. However, response rates were notably lower for the subsets of patients who had prior surgery and radiation and those who had metastatic disease [10]. In a number of randomized phase III trials performed in the 1990s, this PF regimen was shown to be superior to single-agent regimens, in terms of response rates but not in terms of meaningful survival advantage, and this gain in response rates was obtained at the cost of more toxicity [30–32].

The phase III trial reported by Forastiere et al. [30] highlights additional important information, which is of use for daily practice. In this study 277 patients were randomized to receive PF, carboplatin–5-FU (CF) or standard dose methotrexate. With respect to response rate, PF scored significantly higher than methotrexate ($P < 0.001$), but the comparison of CF with methotrexate was of only borderline significance ($P = 0.05$). Median response duration and median survival time were similar for all three treatment groups. In support of this difference between PF and CF, it is to be mentioned that the CF combination also induced fewer responses than the PF regimen in a randomized phase III trial in the neoadjuvant setting [33]. Moreover, there was no difference in response rate in a randomized comparison of carboplatin plus methotrexate versus single-agent methotrexate [34]. Taken together, these data clearly indicate that carboplatin is less active than cisplatin in the treatment of SCCHN.

*platinum–taxane combinations.* Of the newer agents, the taxanes have been studied most extensively in combination chemotherapy regimens [20, 35–39]. Regimens with carboplatin and paclitaxel did not seem to be much different from regimens with cisplatin and paclitaxel. However, a recently reported phase II trial in R/M-SCCHN (including patients with ECOG 0–2) conducted by the Southwest Oncology Group indicated only moderate activity of carboplatin plus docetaxel.

The paclitaxel plus cisplatin (PP) combination was directly compared with the PF regimen in the Intergroup trial E1395
two-drug and three-drug platinum–taxane combinations. The TPF regimen, which consists of docetaxel, cisplatin and infusional 5-FU, has become the new standard for induction chemotherapy in the locoregionally advanced disease setting since the publication of the TAX323/EORTC24971 (Europe) and TAX324 studies (USA) [40, 41]. There is a temptation to use this regimen or other three-drug regimens also in the R/M disease setting. Janinis et al. [42] observed an overall response rate of 44%, a median time to progression of 7.5 months and a median OS of 11 months. Of note, despite the use of G-CSF in this study, febrile neutropenia occurred rather frequently (in 15% of patients). The TIP and TIC regimens reported by Shin et al. [36, 37], which consist of paclitaxel, ifosfamide and cisplatin (TIP) or carboplatin (TIC), are the most active regimens ever tested in the MD Anderson Cancer Center. Response rates of 58% and 59% were reported with CR rates of 17%, in both regimens of long duration (median 15.7+ months with TIP and median 9.7 months with TIC), but an unacceptably high incidence of febrile neutropenia (27% with TIP and 30% with TIC). Our personal experience with the DIP regimen (docetaxel, ifosfamide, cisplatin) in the locoregionally advanced disease setting [43], showing responses in 95% (after two cycles), 82% grade 4 neutropenia and 36% febrile neutropenia are in line with these observations. Overall, it can be concluded that platinum–taxane-containing triplets induce high response rates, also in patients with R/M-SCCHN. However, they are associated with substantial hematologic toxicity and a high complication rate.

As these triplets have never been directly compared with PF in a randomized phase III study in this setting, they should not be recommended outside clinical trials. Moreover, as none of the combination chemotherapy regimens demonstrated an OS benefit when compared with single-agent methotrexate, cisplatin or 5-FU, combination chemotherapy should preferably be used in younger patients with good PS and with symptomatic disease who require prompt symptom relief.

targeted therapies

Several biological therapies have been chosen in head and neck cancer patients because of their different mechanism of action, greater selectivity (target of action is overexpressed as compared with normal tissue), different toxicity profile or because they play a role in carcinogenesis [9, 44]. These include drugs that target growth factors and their receptors, signal transduction, cell cycle control, prostaglandin synthesis, protein degradation, hypoxia and angiogenesis [45]. As randomized trials leading to a further improvement in outcome have only been performed with drugs targeting the growth factors and/or growth factor receptors, in particular those of the HER family, this will be the main focus of this part of the article.

epidermal growth factor receptor and ErbB2. The epidermal growth factor receptor (EGFR) inhibitors are of particular interest, because EGFR and its ligand TGF-α are overexpressed in the vast majority of cases of SCCNH. In contrast, ErbB2 expression in SCCNH ranges between 40% and 60% [46]. EGFR overexpression and increased EGFR copy number have been related to poor prognosis in patients with SCCNH [47, 48]. Its prognostic role is more specifically related to the treatment received, such as radiotherapy [47, 49] and chemotherapy [50]. Recently it was found, however, that both EGFR expression and FISH determination were not predictive of response to anti-EGFR therapy with cetuximab [51].

Two of the potential EGFR targeting strategies are currently in clinical use: monoclonal antibodies (mAbs) directed at the extracellular domain of the receptor, and the small molecule and ATP-competitive tyrosine kinase inhibitors (TKIs). Table 1 summarizes some important EGFR inhibitors under clinical investigation in R/M-SCCHN. EGFR-activated signaling pathways and the effect of activation on cell proliferation and survival are well documented [52]. Ligand binding to the EGFR

Table 1. Selection of relevant EGFR-targeting agents under clinical investigation in SCCNH

<table>
<thead>
<tr>
<th>Agent</th>
<th>Toxicity</th>
<th>Monoclonal antibodies</th>
<th>Tyrosine kinase inhibitors</th>
</tr>
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<tbody>
<tr>
<td>Cetuximab</td>
<td>IMC225</td>
<td>Chimeric human/murine</td>
<td>FGFR</td>
</tr>
<tr>
<td>Matuzumab</td>
<td>EM172000</td>
<td>Humanized mouse</td>
<td>FGFR</td>
</tr>
<tr>
<td>Nimotuzumab</td>
<td>h-R3</td>
<td>Humanized mouse</td>
<td>FGFR</td>
</tr>
<tr>
<td>Zalutumumab</td>
<td>2F8</td>
<td>Human</td>
<td>FGFR</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>ABX-EGF</td>
<td>Human</td>
<td>FGFR</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>ZD1839</td>
<td>Reversible</td>
<td>EGFR</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>OSI-774</td>
<td>Reversible</td>
<td>EGFR</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>PKI-166</td>
<td>Reversible</td>
<td>EGFR/EGFR</td>
</tr>
<tr>
<td>Canertinib</td>
<td>GW-572016</td>
<td>Reversible</td>
<td>EGFR/EGFR</td>
</tr>
<tr>
<td>PKI-0033</td>
<td></td>
<td>Irreversible</td>
<td>EGFR</td>
</tr>
</tbody>
</table>

GI, gastrointestinal.
is followed by stimulation of a number of different signal transduction cascades, including the mitogen-activated protein kinase (MAPK) pathway and the phosphatidylinositol 3-kinase (PI3K)–Akt pathway. The mAbs and TKIs act at different points on the pathway to disrupt signaling. However, it is likely that the effects of these agents are not mediated by disruption of EGFR signaling pathways alone. Also, antibody-dependent cellular cytotoxicity (ADCC) is thought to be an important mechanism of action, but for a long time it was thought that this only referred to IgG1 mAbs [53, 54]. However, very recently it was discovered that also human IgG2 mAbs against EGFR effectively trigger ADCC but, in contrast to IgG1, only by cells of the myeloid lineage [55]. The ability of many EGFR inhibitors to enhance the effects of radiation and/or chemotherapy has been demonstrated both in vitro and in vivo [56]. In vitro and in vivo data indicate that the combined use of an EGFR-targeted mAb and a TKI increases the impact of either agent alone on downstream signaling, apoptosis, proliferation and tumor (xenograft) growth [57, 58], and this may be of interest for the clinical situation, in particular for the R/M disease setting.

**monoclonal antibodies**

cetuximab. The best-studied mAb thus far is cetuximab, which is a human–murine chimeric immunoglobulin G1 (IgG1) mAb, which competitively binds to the extracellular domain of the EGFR. Cetuximab has been tested in R/M-SCCHN, either in second-line therapy after failure of platinum-based chemotherapy or in first-line therapy in combination with platinum-based chemotherapy. Moreover, it has been tested as part of the combined modality treatment of locoregionally advanced SCCHN. This latter application is beyond the scope of this article.

cetuximab in second-line therapy. Three phase II trials examined the role of cetuximab in platinum-refractory or platinum-resistant disease. All patients received cetuximab intravenously (i.v.) at an initial loading dose of 400 mg/m² followed by weekly 250 mg/m² [59–61]. In two of these studies cetuximab was added to the platinum compound that was reintroduced [59, 60], in one study cetuximab was given alone [61]. There was a remarkable similarity in outcome in these three studies. Responses were seen in 10%–13% of patients, DC was observed in 46%–55% of patients and median OS was 5.2–6.1 months. This similarity, irrespective of whether cetuximab was administered as a single agent or added to a platinum-based regimen, indicates that the observed responses were attributable to cetuximab alone rather than to the reversal of platinum resistance by cetuximab.

Interestingly, the median survival of 5–6 months achieved with cetuximab in platinum-refractory disease was reaching a level very close to that with first-line therapy in randomized trials and represented an increase in survival of 2.5 months compared with platinum-refractory historical controls [62]. Based on these results and particularly considering the fact that ~50% of the patients showed DC, cetuximab monotherapy seems to be a good option for patients with R/M-SCCHN who have progressed on platinum-based chemotherapy. It is also approved for that indication in the USA.

cetuximab in first-line therapy. Table 2 summarizes the data on cetuximab in first-line therapy, showing a remarkable consistency in efficacy in patients with R/M-SCCHN, whether treated with platinum-based chemotherapy [63–65], taxane-based chemotherapy [66] or platinum–taxane-based chemotherapy [67]. Burtness et al. [63] assigned 117 patients to cisplatin 100 mg/m² every 4 weeks either with weekly cetuximab or with weekly placebo. The primary end point of this study was PFS. The study was designed to detect a difference in median PFS of 2 months i.e. 2 months with cisplatin plus placebo and 4 months with the experimental arm. However, the observed median PFS in the control arm was longer than expected (2.7 months). The median PFS in the cetuximab arm was 4.2 months and that difference did not reach statistical significance (P = 0.09). In fact, the actual power to detect a 2-month difference in this situation was only 50%. The OR rate was 26% in the experimental arm versus 10% in the control arm (P = 0.03). Median OS was not significantly different (9.2 months versus 8 months, P = 0.21). Development of cetuximab-related skin toxicity was associated with an improved OS [hazard ratio (HR) 0.42, P = 0.01]. In the EXTREME study [65] 442 patients were randomized to receive either chemotherapy alone (cisplatin 100 mg/m² or carboplatin AUC 5 mg/ml/min on day 1 followed by 5-FU 1000 mg/m²/day for 4 days) or the same regimen combined with weekly cetuximab (initial loading dose of 400 mg/m² followed by weekly doses of 250 mg/m²). Cycles were repeated every 3 weeks for a maximum of six cycles. Thereafter, in the combined arm, cetuximab was continued as a single agent until disease progression or unacceptable toxicity, whichever came first. No crossover was permitted in this study. Excluded were patients who had received prior chemotherapy except when this had

<table>
<thead>
<tr>
<th>Author/study</th>
<th>Phase</th>
<th>Regimen</th>
<th>ORR (%)</th>
<th>PFS (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burtness et al. (2005) [63]</td>
<td>III</td>
<td>CDDP + cetuximab</td>
<td>26*</td>
<td>4.2</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CDDP + placebo</td>
<td>10</td>
<td>2.7</td>
<td>8.0</td>
</tr>
<tr>
<td>Bourhis et al. (2006) [64]</td>
<td>I/II</td>
<td>PF + cetuximab</td>
<td>36</td>
<td>5.1</td>
<td>9.8</td>
</tr>
<tr>
<td>Vermorken et al. (2008) [65]</td>
<td>III</td>
<td>PF + cetuximab</td>
<td>36**</td>
<td>5.6**</td>
<td>10.1***</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PF</td>
<td>20</td>
<td>3.3</td>
<td>7.4</td>
</tr>
<tr>
<td>Hitt et al. (2007) [66]</td>
<td>II</td>
<td>Paclitaxel + cetuximab</td>
<td>60</td>
<td>5.0</td>
<td>NR</td>
</tr>
<tr>
<td>Buentzel et al. (2007) [67]</td>
<td>II</td>
<td>Paclitaxel + cetuximab</td>
<td>56</td>
<td>5.0</td>
<td>8.0</td>
</tr>
</tbody>
</table>

CDDP, cisplatin; PF, platinum (cis or carbo) + 5-fluouracil; PFS, progression-free survival; ORR, objective response rate; OS, overall survival; *P = 0.03; **P < 0.001; ***P = 0.04.
been part of their primary treatment provided this chemotherapy was ended at least 6 months before inclusion in the study. The primary end point was OS. The addition of cetuximab to platinum–5-FU significantly prolonged the median OS from 7.4 months in the chemotherapy-alone group to 10.1 months in the group that received chemotherapy plus cetuximab (HR for death, 0.80; 95% CI 0.64–0.99; \( P = 0.04 \)). The addition of cetuximab also prolonged the median PFS from 3.3 to 5.6 months (HR for progression, 0.54; \( P < 0.001 \)) and increased the response rate from 20% to 36% (\( P < 0.001 \)). The beneficial effect was evident in both the patients treated with cisplatin–5-FU and the patients treated with carboplatin–5-FU, although also in this study response rates with carboplatin–5-FU were below those obtained with cisplatin–5-FU independent of the treatment arm. Moreover, protocol-defined subgroup analyses showed that the beneficial effects of adding cetuximab to platinum–fluorouracil chemotherapy on OS and PFS were evident in nearly all subgroups analyzed. The most common grade 3 or 4 adverse events in the chemotherapy-alone and cetuximab groups were anemia (19% and 13%, respectively), neutropenia (23% and 22%) and thrombocytopenia (11% in both groups). Sepsis occurred in nine patients in the cetuximab group and in one patient in the chemotherapy-alone group (\( P = 0.02 \)). There were 11 cases of grade 3 or 4 hypomagnesemia in the cetuximab group, as compared with three cases in the chemotherapy-alone group (\( P = 0.05 \)). Of the 219 patients receiving cetuximab, 9% had grade 3 skin reactions and 3% had grade 3 or 4 infusion-related reactions. There were no cetuximab-related deaths.

This is the first time in >30 years that superiority (in terms of survival) of a new regimen over standard platinum-based combination chemotherapy has been observed. Cetuximab and platinum-based chemotherapy is now considered as a new standard for the treatment of R/M-SCCHN for those who are able to tolerate platinum-based combination chemotherapy regimens [7, 68].

Panitumumab. Panitumumab (ABX-EGF) is a fully human IgG2 antibody which binds very strongly to the receptor [44, 69]. It blocks ligand binding and induces internalization of the receptor but no receptor degradation. Side-effects include pruritus, skin rash, dyspnea, fatigue, abdominal pain, asthenia and diarrhea. Panitumumab at a weekly dose of 2.5 mg/kg has acceptable tolerability and encouraging clinical activity in patients with a variety of tumor types. Its pharmacokinetic profile allows more convenient 3-weekly administration (9 mg/kg). Three studies with panitumumab in the R/M disease setting are of interest, i.e. the PRISM study, the PARTNER study and the SPECTRUM study. The PRISM study is a phase II study with single-agent panitumumab in second-line therapy, the PARTNER study is a randomized phase II study in first-line therapy studying docetaxel plus cisplatin with or without panitumumab and in the SPECTRUM trial, similar patients to those in the EXTREME trial were randomized to receive cisplatin–5-FU with or without panitumumab. Enrolment in this latter trial has been completed. The combination was safe and efficacy data are awaited in 2010 [70].

Zalutumumab. Zalutumumab [44] is also a fully human IgG1 EGFR-directed mAb. The frequency of acneiform rashes with this compound increases with dose. This mAb is currently undergoing phase III testing in patients who failed standard platinum-based chemotherapy versus BSC [71]. However, in this so-called ZALUTE trial a great majority of patients in the BSC arm (78%) received weekly methotrexate as allowed by the protocol. There was a strong trend in favor of the zalutumumab arm for OS (median 6.7 versus 5.2 months, \( P = 0.0649 \)), which was the primary end point of the study. There was a statistically highly significant difference in PFS in favor of the experimental arm (median 9.9 versus 8.4 weeks; \( P = 0.0010 \)). The results of this trial confirm the activity of EGFR-directed mAbs in patients with platinum-refractory SCCHN [72].

Matuzumab. Matuzumab is a humanized IgG1 mAb that in a phase I dose escalation study in stage III/IV laryngeal and hypopharyngeal cancer showed that fever and transient elevations of liver enzymes were the most frequently observed treatment-related adverse events [73]. A weekly dose of 200 mg, based on pharmacokinetic findings, was selected for further studies. No data of randomized trial in R/M-SCCHN are available.

Nimotuzumab. Nimotuzumab [44] is also a humanized IgG1 mouse antibody. Preliminary data indicate that therapeutic levels of nimotuzumab can be achieved without eliciting skin toxicity, which is the most common side-effect of the other anti-EGFR-directed antibodies. Nimotuzumab has a lower receptor affinity than e.g. panitumumab, cetuximab or matuzumab, and although there is no clinical evidence that higher affinity to the receptor leads to greater efficacy, stronger binding clearly leads to higher toxic effects, i.e. a higher incidence of acneiform rash [74]. A phase IIB clinical study in Indian patients with advanced (stage III and IVa) SCCHN showed only few skin reactions, including urticaria and pruritis, but did show some headache, hypertension and fluctuation in blood pressure [75, 76]. No data on R/M-SCCHN patients are available.

**tyrosine kinase inhibitors**

**single-agent use.** Table 3 shows the results of studies with tyrosine kinase inhibitors (TKIs) used as single agents. As a reference, also the data with cetuximab in platinum-refractory SCCHN are given [61]. The study population in most of the studies is a mixture with respect to prior platinum treatment of R/M-SCCHN and therefore cannot be considered fully platinum refractory. With a few exceptions (see below) the results with TKIs have been disappointing. Single-arm trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase</th>
<th>Reference</th>
<th>Response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>II</td>
<td>Vermorken 2007 [61]</td>
<td>13</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>II</td>
<td>Soulieres 2004 [77]</td>
<td>4.3</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>II</td>
<td>Cohen 2003 [78]</td>
<td>10.6</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Cohen 2005 [79]</td>
<td>1.8</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>Kirby 2006 [80]</td>
<td>8.5</td>
</tr>
<tr>
<td></td>
<td>III*</td>
<td>Stewart 2009 [81]</td>
<td>7.9</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>II</td>
<td>Abidoye 2006 [82]</td>
<td>0</td>
</tr>
<tr>
<td>BIBW 2992</td>
<td>II*</td>
<td>Seiwert 2010 [83]</td>
<td>21.7</td>
</tr>
</tbody>
</table>

*Randomized studies
with gefitinib and erlotinib showed response rates ranging from 0% (in chemotherapy-refractory disease) to 15% (in untreated R/M disease patients) and a median PFS of ~3.5 months [77–80]. Drug toxicity was generally mild, consisting of skin rash and diarrhea, more frequent at higher dosages. It has been suggested, based on some of these single-arm studies, that outcome might be related not only to the occurrence and severity of the skin reaction, but also to the dose used. This latter aspect was tested in a large phase III trial (1839 IL/0704; IMEX) in which 482 patients with R/M-SCCHN, unresponsive to platinum or unfit for platinum, were randomized in a three-arm study to receive either gefitinib 250 mg/day or gefitinib 500 mg/day or methotrexate 40 mg/m² i.v. weekly [81]. Neither gefitinib 250 mg/day nor gefitinib 500 mg/day improved survival compared with single-agent methotrexate. OR rates were 2.7%, 7.6% and 3.9%, respectively and median OS was 5.6, 6 and 6.7 months, respectively. Tumor bleeding was observed more frequently in patients treated with gefitinib than those treated with methotrexate.

Single-agent lapatinib (1500 mg/day) was associated with disappointing activity (no ORs) in a phase II study in 42 patients with R/M disease, 15 of whom had previously received treatment with an EGFR inhibitor [82]. Cohen et al. [84] reviewed individual patient data from five clinical trials of lapatinib, cetuximab or gefitinib to determine whether there are clinical characteristics that are associated with clinical benefit. PS (P = 0.04), older age (P = 0.02), and development of rash (P < 0.01), diarrhea (P = 0.03) or oral side-effects (P = 0.02) were independently associated with clinical benefit. Older age, better PS and development of rash were associated with longer PFS and OS. EGFR mechanistic toxic effects that developed during therapy were also highly associated with benefit and indicate a relationship between drug exposure and outcome [84]. During ASCO 2010, interesting results were reported with BIBW 2992, a highly potent inhibitor of EGFR/erbB1 and erbB2. It retains activity for EGFRvIII mutation and provides a sustained blockage of receptor and inhibition of tumor cell proliferation. Seiwert et al. [83] presented results of a randomized, open-label, phase II study of BIBW 2992 versus cetuximab in R/M-SCCHN patients after failure of platinum-containing therapy. The primary end point of that study was tumor shrinkage of target lesions before any crossover. Diarrhea, dehydration, epistaxis and asthenia occurred more frequently with BIBW 2992, but also tumor shrinkage occurred more frequently with BIBW 2992 than with cetuximab (OR 21.7% versus 13.3%). The DC was comparable (56.7% versus 61.7%). Median PFS with BIBW 2992 was 16 weeks (95% CI 10–19) and 10 weeks (95% CI 8–17) with cetuximab. BIBW is recommended for patients who do not respond to cetuximab, the first clinically available EGFR-directed mAb, to a standard chemotherapy regimen (platinum–5-FU) leads to an important survival benefit and this, with support of an additional smaller study in the USA, has changed practice.

treatment of R/M-SCCHN: summary

Unfortunately, the outcome of patients with R/M-SCCHN is still dismal. In the absence of distant metastatic disease, salvage surgery and re-irradiation should be considered. When considering re-irradiation important prognostic factors, such as interval from previous radiation, recurrent tumor stage and tumor bulk should be taken into account next to the re-irradiation dose. It is very doubtful whether patients with both co-morbidity and organ dysfunction might benefit from such an approach. The use (and also choice) of systemic therapies is very much dependent on the general condition of the patient, his/her age and whether he/she has symptomatic disease. Unfavorable prognostic factors for survival are weight loss, an ECOG PS of 1 (versus 0), a primary tumor in the oral cavity or hypopharynx, prior radiotherapy and good/moderate tumor cell differentiation. It seems of importance to take these factors into account when performing trials.

None of the trials performed in the past, even those with reasonable sample size, have shown that aggressive platinum-based combination chemotherapy regimens lead to survival benefit when compared with single-agent methotrexate, cisplatin or 5-FU in R/M disease. After decades without real progress, a recent European randomized trial showed that adding cetuximab, the first clinically available EGFR-directed mAb, to a standard chemotherapy regimen (platinum–5-FU) leads to an important survival benefit and this, with support of an additional smaller study in the USA, has changed practice.

disclosures

J.B. Vermorken has participated in advisory boards of Merck-Serono, Amgen, Genmap, Sanofi-aventis and Oncolytics.

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