Optimizing approaches to head and neck cancer. Metastatic head and neck cancer: new options

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Introduction
In 2002 there were about 144 000 new cases of head and neck squamous cell cancer (HNSCC) in Europe and 69 000 deaths, making it the seventh leading cause of cancer death [1]. HNSCC arise from the mucosa of the upper aerodigestive tract. They include cancers of the oral cavity, the pharynx (naso-, oro- and hypopharynx), the larynx and the paranasal sinuses. The head and neck region includes different tissues so that other kinds of neoplasms occur there, such as cancer of the salivary glands and rare histotypes of the paranasal sinuses and thyroid cancer. In this paper we will focus on HNSCC.

HNSCC
Approximately 60–65% of patients with head and neck cancer can be cured with surgery and/or radiotherapy. Patients with early stage (stages I and II) disease are treated with single-modality treatment (either surgery or radiotherapy), while patients with a more advanced disease (stages III and IV) need a combined approach such as extensive surgery and radiotherapy or chemoradiation. However, only a smaller proportion of them may be cured (30%). Causes of treatment failure are locoregional recurrences (60%), followed by metastatic disease (up to 30%) and second primaries [2]. An individual patient’s prognosis depends on the tumour site, its extension, nodal involvement and grade [3].

Prognostic factors of recurrent and/or metastatic HNSCC
Several clinical prognostic factors have been proposed to try to define patients who are most likely to benefit from palliative chemotherapy. Traditionally adequate PS, a long time interval between primary and recurrence, response to palliative chemotherapy and poorly differentiated histotype were all related to a better outcome [4–6]. More recently an analysis of 400 patients accrued in two Eastern Cooperative Oncology Group (ECOG) prospective trials with cisplatin-based first-line chemotherapy, was able to define five prognostic factors that were significantly associated with 2-year survival. They included response to palliative chemotherapy, PS, white race, poorly differentiated squamous histotype and no prior radiotherapy [7]. On this basis the authors proposed to use single factors within a global score (0–2 vs ≥3) that allowed the definition of two distinct survival curves with a median survival of 0.98 year for the favourable score vs 0.52 year. It is noteworthy that approximately two-thirds of the patients fell within the adverse scoring with a very poor expected survival, underlying again the need for novel active treatments for this patient population.

Treatment of recurrent and/or metastatic HNSCC: chemotherapy
For decades the standard of care for palliative management of recurrent and/or metastatic HNSCC has been either the combination of cisplatin and fluorouracil or a monochemo-therapy with methotrexate or cisplatin. As a first-line therapy this combination offers a slightly superior response rate, which unfortunately does not translate into an improvement in survival over monochemotherapy alone, at the expense of more toxicity.

Several Phase II studies included taxanes in monotherapy in a first-line recurrent and metastatic setting—in particular taxotere, 100 mg/m² every 21 days or weekly 40 mg/m² with response rates ranging from 21% and 42% [8–12]. In only one study was it given weekly within a Phase II randomized trial enrolling 57 patients comparing it with methotrexate, with similar results in terms of progression-free survival (PFS) and overall survival (OS), slightly more responses (27% vs 15%) and a significant increase in grade 3–4 toxicity (40% vs 20%) [13]. Taxotere was also combined with fluorouracil [14, 15] or gemcitabine [16] with a response rate (RR) of approximately 20%, similar to that obtained with docetaxel monotherapy, suggesting that these combinations are of little interest. On the contrary, when docetaxel was combined with cisplatin the RRs were impressively high, ranging from 33% to 53% [17–21]. Different schedules were tested: in general, the cisplatin dose was maintained at 75 mg/m² and docetaxel was given at 100 or 75 mg/m². A more recent trial combined the 3-week schedule of docetaxel and cisplatin with erlotinib, with a very high RR (67%), in spite of a significant grade 3–4 toxicity, including neutropenia, diarrhoea and dehydration [22]. These findings suggest that the combination...
of target therapy to already consolidated polychemotherapy schedules may display very high toxicity, thus underlining the need not to use these drugs outside clinical studies.

Weekly taxol was associated with weekly cetuximab in 46 patients with a very high RR reaching 70% and acceptable toxicity [23].

Only two randomized studies were performed comparing the classical cisplatin plus fluorouracil schedule with cisplatin plus taxol [24] and the study V233, in which cisplatin and docetaxel were used as the experimental arm. The first trial showed no difference in terms of OS and RR. The second trial has never been published, possibly because it was negative. In the study comparing PF with cisplatin and taxol, toxicities were similar, although haematological and gastrointestinal toxicity were more common in the PF arm. Therefore the combination of taxol and cisplatin can be considered as a first-line treatment with a better toxicity profile, although it should be stressed that any combination is associated with significant morbidity and therefore should be reserved for selected patients.

With the advent of new molecularly targeted agents, such as epidermal growth factor receptor (EGFR) inhibitors, the number of therapeutic options in this field has increased. Targeting EGFR in HNSCC is a rational approach sustained by a large body of evidence that supports the relevance of the target. EGFR overexpression and increased EGFR copy number [25] have been related to poor prognosis in patients with HNSCC. More recently, its prognostic role was more specifically related to the treatment received, such as radiotherapy [26, 27], and chemotherapy [28]. The role of EGFR overexpression and FISH determination in predicting the response to anti-EGFR treatment is less clear.

**treatment of recurrent and/or metastatic HNSCC: EGFR-tyrosine kinase inhibitors**

Selective agents targeting EGFR in HNSCC are under clinical evaluation, the most advanced agent is cetuximab, along with gefitinib. Both have completed phase III evaluation.

**cetuximab**

Burtness and colleagues published a phase III randomized trial comparing cisplatin plus cetuximab or placebo in previously untreated patients [29]. The RR for the combination was higher (23% vs 9%), without translating into a survival benefit. Unfortunately the study was underpowered to detect any survival difference. In this trial, the development of skin rash with cetuximab represented a favourable prognostic factor. Surprisingly, a marginally statistically significant benefit in survival was noted in the subset of patients with low to moderate EGFR expression compared with those who were high staining for EGFR. The interpretations they gave for the mechanisms behind this observation, such as insufficient drug being able to saturate highly expressed receptor, need to be validated; to date no specific marker for predicting tumour response to anti-EGFR therapy has been found.

A phase III trial, which studied the role of cetuximab to standard platinum (or carboplatin) and 5-fluorouracil chemotherapy has been reported in abstract form [30]. Median PFS has been prolonged by 2.6 months, while overall prolongation of survival was 2.7 months in the cetuximab arm, thus showing the first evidence in the last 25 years of survival gain offered by systemic therapies in recurrent and metastatic head and neck cancer patients. The RR was in favour of the experimental arm, 36% vs 20%, indicating that prolongation of life is occurring for a consistent fraction of responding patients. It is intuitive how response can be important for this cancer population. Preliminary subgroup patient analysis that included age, PS, tumour primary sub-site, histological differentiation, treatment with cisplatin or carboplatin and previous chemotherapy scheduling showed a benefit in term of PFS for each of them. With respect to OS, subgroup analysis of patients with deteriorated PS < 80 and age > 70 years shows that they seem not to benefit from the association of cetuximab. Nonetheless, both criteria seem to be more associated with the well-known clinical limitation of treating such patients with polychemotherapy rather than an insufficient activity of cetuximab. Importantly, toxicity seemed not to increase on adding cetuximab to standard first-line polychemotherapy, although it should be stressed that in any case polychemotherapy should be reserved for selected and fit recurrent head and neck cancer patients. In this study quality of life was measured, and according to the preliminary analysis of global health status, social functioning, swallowing and pain scores there was no significant impact on it by adding cetuximab to classical P (or Carbo)F.

A phase II study reported in abstract form showed encouraging results on adding cetuximab to paclitaxel as first-line treatment for recurrent/metastatic disease [23]. In the platinum-resistant patients the RR of cetuximab in monotherapy or in combination with cisplatin was similar (10% vs 13%) [31–33]. In the light of these data, cetuximab seems to have an intrinsic activity rather than just reversing the platinum resistance function.

**small molecules**

Gefitinib was studied in monotherapy in the three phase II studies that have been published so far, showing a RR varying from 1.4% to 11% and a median PFS of approximately 3.5 months [34–36]. A dose–response relationship was identified between 250 mg and 500 mg daily. Drug toxicity was mild, consisting of skin rash and diarrhoea, more frequent at higher doses. Response was associated with the development of skin toxicity.

Data from a phase III study comparing gefitinib at two different doses with methotrexate monochemotherapy in RM disease have recently been presented. No significant difference in survival could be observed among the three treatment groups, with a median survival of 5.6 (gefitinib 250 mg/day), 6.0 (gefitinib 500 mg/day) and 6.7 (methotrexate) months [37]. Tumour haemorrhage was observed more frequently in patients treated with gefitinib. Erlotinib in monotherapy showed similar RR of 4.3% and median PFS of 4 months [38]. By adding it to cisplatin, a RR of 21% was obtained, with a median OS of 7.9 months [39]. These results were obtained in a population of platinum-sensitive
patients and are similar to those achieved by the combination of cisplatin and cetuximab [29].

Combination of the tyrosine-kinase inhibitors gefitinib or erlotinib with cisplatin plus docetaxel in first-line treatment of RM HNSCC produced interesting results in small groups of patients [22,40]. Combination of tyrosine-kinase inhibitors with other different targeted therapies such as gefitinib plus celecoxib, erlotinib plus bevacizumab, or as single agents (sorafenib, lapatinib) has been studied in small phase I–II trials [41–44].

disclosures
Lisa Licitra has been involved in advisory boards with Merck Serono, GlaxoSmithKline, Amgen.

references