Cetuximab therapy for patients with advanced squamous cell carcinomas of the head and neck

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Cetuximab increases overall survival in patients with recurrent or metastatic squamous cell carcinomas of the head and neck. Reasonable treatment strategies include the use of first-line platinum, 5-fluorouracil and cetuximab combination, or cetuximab used following progression after a platinum-based regimen.

Summary

We discuss the results of the phase III EXTREME trial. In this study by Vermorken et al. (**Platinum-based chemotherapy plus cetuximab in head and neck cancer**. *N Engl J Med* 359:1116–27), 442 untreated patients with advanced squamous cell carcinomas of the head and neck (SCCHN) were randomly assigned to receive platinum and 5-fluorouracil with or without cetuximab. Median overall survival, the primary endpoint of the trial, was longer in the cetuximab arm (10.1 months vs 7.4 months; *P*=0.04). This is the first phase III trial in over two decades to show a survival advantage in patients with SCCHN not amenable to curative treatment. However, it raises several considerations for clinical practice and research, such as the best choice of chemotherapy to combine with cetuximab, sequencing of cetuximab with chemotherapy, predictive markers of benefit from cetuximab, and implications for patients with locally advanced, potentially curable disease.

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Squamous cell carcinomas of the head and neck (SCCHN) that recur after definitive local therapy, or have distant metastases at presentation, are often treated with palliative chemotherapy consisting of a single-agent cytotoxic drug or platinum-based doublets. Although combination chemotherapy enhances response rates compared with single-agent cisplatin or methotrexate, no combination chemotherapy regimen has been demonstrated to improve overall survival (OS).[1] The EXTREME study was the first phase III trial in over two decades to exhibit a survival advantage in patients with SCCHN not amenable for curative treatment.[2] In EXTREME, 442 patients with untreated recurrent or metastatic SCCHN were randomly allocated to receive up to six cycles of combination chemotherapy (cisplatin or carboplatin) and 5-fluorouracil, with or without cetuximab (400 mg/m^2 initial dose, followed by 250 mg/m^2 weekly). In the experimental arm, cetuximab was continued beyond chemotherapy until disease progression.[2] The primary end point of the trial – improvement in OS – was met; median OS in the cetuximab arm was 10.1 months, compared with 7.4 months in the chemotherapy-alone arm (*P*=0.04). Prolonged median progression-free survival, increased response rates, and time to treatment failure were also observed in the

cetuximab arm. The toxicity profile was modest, with grade 3–4 skin reactions (9% vs <1%), sepsis (4% vs <1%) and hypomagnesaemia (5% vs 1%) occurring more frequently in the cetuximab arm.[2] This trial provides important findings in a disease with limited treatment options; however, it raises several considerations for routine clinical practice and future research directions.

The authors opted for platinum and 5-fluorouracil as the backbone chemotherapy – a regimen widely used in European countries. The use of carboplatin could have accounted for the somewhat lower than expected response rate observed in the control arm (20% in EXTREME[2] versus ~30% in other trials using cisplatin-based combinations[1]). Nonetheless, the trial design was realistic in allowing for regimens that could be easily translated into general practice and, in our view, the use of carboplatin does not diminish the significance of the findings. Physicians in the US prefer platinum–taxane doublets for metastatic SCCHN. To our knowledge, there are no phase II data on the combination of cetuximab, platinum and a taxane in this setting; however, in early studies of locally advanced disease, regimens containing cetuximab and a taxane have produced impressive response rates (97%–100%) and an acceptable toxicity profile when given as induction therapy.[3,4] Cisplatin and docetaxel have been combined with other EGFR inhibitors in phase II trials of metastatic SCCHN with promising results.[1,5] Erlotinib or gefitinib in these studies were also continued after chemotherapy until disease progression. Whether the maintenance treatment adds to survival in this setting is unknown. If tyrosine kinase inhibitors are found to be as effective as cetuximab in phase III trials of metastatic SCCHN, these agents could have important cost and convenience advantages during and after chemotherapy.

Cetuximab enhances the cytotoxic effects of chemotherapy and has single-agent anti-neoplastic activity *in vitro* and *in vivo*.[6] It has been approved by the FDA as monotherapy for treatment of patients with SCCHN who progress after platinum-based therapy. This indication is based on a single-arm, phase II study that demonstrated a 13% response rate to cetuximab in 103 patients with platinum-refractory tumours.[7] In the EXTREME trial, the difference in response rates for the two groups was in a similar range of 16% (36% for the cetuximab arm versus 20% for the control arm, $P<0.001$), and only 6% of patients in the control arm received cetuximab after study completion.[2] These data raise the question whether benefits from cetuximab could have potentially been achieved with a sequential approach (i.e. delivering cetuximab upon progression after chemotherapy), thus sparing patients the additional toxicity of combination therapy. The lack of randomised trials of cetuximab versus best supportive care precludes a definitive conclusion regarding the survival benefits of a sequential regimen with these agents. In light of the current data, one could consider both the concurrent and sequential approaches acceptable in this setting.

In a phase III study of radiotherapy with or without cetuximab for locally advanced SCCHN, patients with oropharyngeal cancers derived the most overall survival benefit from cetuximab, as opposed to those with laryngeal and hypopharyngeal cancers.[8] In EXTREME, oral cavity cancers had a lower hazard ratio for death than those in the oropharynx, larynx and hypopharynx.[2] However, at this time, patients should not be excluded from consideration of cetuximab therapy on the basis of the primary tumour site alone. Another important feature of EXTREME was the availability of tissue for EGFR staining as one of the inclusion criteria. Protein expression of EGFR, as assessed by immunohistochemistry, has not been correlated with outcome in the EXTREME trial[2] or other trials of cetuximab.[6] Nonetheless, mandatory tissue availability at study entry ensures collection of biospecimens for potential use in future correlative studies of predictive/prognostic markers (e.g. KRAS mutation and resistance to cetuximab in colorectal cancer).[6]

The EXTREME trial provides evidence that EGFR inhibition alters the natural history of SCCHN, and that EGFR is an effective therapeutic target. As cetuximab enhances response rates, an even stronger rationale now exists for combining cetuximab with chemotherapy regimens in the induction setting. Pilot trials of induction combination chemotherapy with cetuximab have produced encouraging results.[3,4] This strategy could potentially result in an increase of the fraction of patients with locally advanced disease who are cured by a multimodality approach.

Details of the references cited in this article can be accessed at www.cancerworld.org/magazine

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