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nature REVIEWS CLINICAL ONCOLOGY

Gastro-oesophageal cancer – is CROSSing over so hard to do?

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Suboptimal studies had established preoperative chemoradiation as the preferred strategy in the management of localised oesophageal cancer (LEC) and gastro-oesophageal cancer. The recent CROSS trial has now demonstrated considerable benefit from preoperative chemoradiation over surgery alone in patients with LEC. But are these results only reinforcing advocates of the preoperative chemoradiation strategy?

This article was first published in ***Nature Reviews Clinical Oncology*** vol. 9 no. 9, and is published with permission.
 doi:10.1038/nrclinonc.2012.122

The incidence of gastro-oesophageal adenocarcinoma has been rising for the past three decades, possibly owing to the dramatic increase in the BMI of adults in many societies, which has led to chronic gastro-oesophageal reflux disease and Barrett's oesophagus.[1–3] Squamous-cell carcinoma remains the most frequent histology in the endemic areas of the world, whereas adenocarcinoma is now the most common form of gastro-oesophageal cancer in the USA and parts of the Western World.[4] Historically, the management of localised oesophageal cancer (LEC) has been a source of intense debate. Complexities in the clinical decision-making for patients with LEC include the location of the primary tumour, histological subtype and tumour grade, clinical T and N stages, length of the tumour, ability of the patient to withstand surgery, and prevailing practice patterns. There may be unity in how to manage early-stage disease endoscopically (for example, stage Tis [carcinoma *in situ*] and T1a tumours), but opinion is divided in terms of how to manage thoracic T2–T3 tumours with any N stage or T1N+ tumours. In patients who can withstand surgery, thoracic LEC is best managed by multimodal therapy – preoperative chemotherapy or preoperative chemoradiation – because the five-year survival rates from primary surgery are dismal,[5] although high-volume centres have reduced surgical mortality considerably.[6] Multidisciplinary evaluation before starting any therapy is encouraged; however, it is not the norm in many countries (such as China and India, where most patients undergo surgery directly). In fact, preoperative chemotherapy for thoracic LEC is largely abandoned in North America but remains popular in many European countries.

Regarding the preoperative chemotherapy strategy, a North American randomised trial of this approach reported no benefit,[7] and a larger British trial from the Medical Research Council demonstrated only marginal benefit.[8] Preoperative chemoradiation, however, may be establishing itself as the strongest contender among all strategies.

Results from the CROSS trial[9] con-

ducted in Europe, have demonstrated considerable benefit from preoperative chemoradiation over surgery alone in selected patients with LEC. Yet the CROSS study may be reinforcing only the subscribers of the preoperative chemoradiation strategy and may not convert the proponents of preoperative chemotherapy or primary surgery. We feel that the report published by van Hagen et al.,[9] which represents the largest trial of its kind, may be transformative, although, we have our doubts about its impact on global approaches to LEC. Van Hagen et al.[9] randomly assigned 368 LEC patients with histologically confirmed squamous-cell carcinoma or adenocarcinoma (tumour stage T1N1 or T2–T3 with any N) to receive preoperative chemoradiation with paclitaxel and carboplatin in combination with 41.4 Gy of 3-D conformal radiation technique in 23 fractions given five days per week (n=180) or surgery alone (n=188). Although the tumours were well staged at baseline (even if no PET was carried out), patients were still selected according to age (18–75 years), weight loss (≤10%), and tumour not exceeding 8 cm in length or 5 cm in width. With a median follow up of 45.4 months, the median overall survival for the group receiving preoperative chemoradiation was 49.4 months versus 24 months for the surgery-only group (HR 0.67, 95%CI 0.495–0.871; P=0.003). The five-year overall survival rate was 47% versus 34%, favouring the chemoradiation group. This benefit was observed in both histological subgroups studied; however, the effect in the adenocarcinoma group (the largest cohort of the two histological subtypes: 275 patients vs 46) was marginal (P=0.049). Chemoradiation did not lead to excessive toxicity. Other benefits from preoperative chemoradiation included a higher rate of R0 resection and, as expected, a higher rate of pathological complete response in the surgical specimen. Data also supported the use of a moderate radiation dose of 41.4 Gy.

The CROSS trial is a well conceived and well-executed study that establishes level 1 evidence for preoperative chemoradiation for thoracic LEC and gastro-oesophageal cancers stage T1N1 or T2–T3 with any N stage. However, we are doubtful that these results will help establish a uniform global strategy for this group of LEC patients. This is in part because van Hagen et al.[9] are not optimistic about the preoperative chemoradiation strategy for patients with thoracic LEC and leave the door open to other options (even though the evidence of the benefit of other options is dubious). What will it take for us to have one global strategy for this group of patients with LEC? The answer to this quandary is unclear. However, those oncologists who prefer preoperative chemoradiation are on firm ground because of the CROSS trial results, and those who believe in surgery first or preoperative chemotherapy have little to base this on. We recommend preoperative chemoradiation as the preferred approach for the group of patients studied in the CROSS trial. We do not endorse surgery first or preoperative chemotherapy under normal clinical conditions, in which there is no contraindication to radiation. It is time to CROSS over.

> “Yet, the CROSS study may be reinforcing only the subscribers of preoperative chemoradiation”

Significant challenges remain when dealing with a difficult disease such as LEC. We must develop strategies that are appropriate for each histological subtype, for each anatomic location of LEC, and for each stage group of LEC. We must exploit the information provided by better imaging, such as PET. We must develop imaging methods that provide highly specific information – those that can image proliferation, apoptosis, hypoxia, receptor proteins, etc. before and after chemoradiation. Circulating tumour cells, mRNA, DNA, and miRNA can also increase our understanding of the aggressiveness of the cancer. We must carry out in-depth analyses of the molecular biology underlying oesophageal and gastro-oesophageal junction cancer and the genetic profile of the patients. We must focus more on methods to enable the immune system to recognise oesophageal and gastro-oesophageal cancer. Finally, we must identify patients who do not require oesophagectomy because their cancer is highly sensitive to chemoradiation.

We feel this can be achieved through establishing validated biomarker signatures and/or sophisticated imaging studies. We must, therefore, strive for oesophageal and gastro-oesophageal junction preservation and customisation of therapy. These are real challenges to deal with while we are debating our therapeutic preferences. These preferences are usually empiric in nature and help only a few patients, while we subject each one of our patients to the toxicity of preoperative therapy and significant life-altering consequences of oesophagectomy.[10] We would be remiss not to mention that we must also

Key point

The CROSS study, which provided excellent evidence in support of preoperative chemoradiation therapy of patients with localised gastro-oesophageal junction cancer, establishes a platform we can build on.

identify adults who are at high risk for developing oesophageal cancer, and detect and treat their cancers early. We may have the roadmap for making progress against LEC, but we seem to be walking in multiple directions. It is time to collaborate.

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Cetuximab dosing by rash – is the scaling of EVEREST meaningful?

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The small EVEREST trial has shown that the concept of guiding cetuximab dose escalation using the clinical parameter of acneiform skin rash is safe. However, as no significant increase of cetuximab efficacy could be observed, data from the ongoing EVEREST II trial must be awaited before dose escalation can be considered for clinical use.

This article was first published online in ***Nature Reviews Clinical Oncology*** vol. 9 no. 10, and is published with permission.
 doi:10.1038/nrclinonc.2012.142

Skin toxicity in patients receiving cetuximab is positively associated with clinical outcome. The EVEREST study was conducted to examine the pharmacodynamics, pharmacokinetics, pharmacogenetics and safety of cetuximab dose escalation in a phase I/II setting in patients with metastatic colorectal cancer.[1] The study specifically investigated whether higher cetuximab doses would lead to a higher occurrence of grade 2 or 3 acneiform rash and superior treatment efficacy. In this study, 89 patients with or without minor (Common Terminology Criteria for Adverse Events [CTCAE] grade 0 or 1) acneiform skin rash after 21 days of receiving the standard dose of cetuximab (250 mg/m² per week after initial 400 mg/m²) were randomly assigned to receive either escalated cetuximab doses of up to 500mg/m² per week or to continue with standard dosing. Patients showing grade ≥2 skin toxicity (n=77) continued standard cetuximab dosing until progression and served as a control group. As with the BOND study,[2] patients were eligible to enrol after irinotecan failure and were administered irinotecan (180 mg/m² every other week) as the chemotherapeutic backbone. The published data of EVEREST[1] focus on the pharmacokinetic parameters, toxicity analyses and efficacy of the different treatment arms.

As expected, cetuximab serum concentrations rose under the influence of increased cetuximab administration. In terms of toxicity, there was no obvious difference in haematological adverse events between patients receiving the standard dose and those receiving the elevated regimen. Considering the non-haematological events associated with therapy, the proportion of patients developing hypomagnesaemia rose, and grade ≥2 cetuximab-related skin toxicities occurred at higher frequencies in the dose-escalated cohort, as predicted. In addition, the authors report efficacy data (objective response rate [ORR], progression-free survival and overall survival) with no significant differences between the different treatment groups. However, a trend towards higher ORR (30% vs 43%) and disease control rate (70% vs 83%) was seen in the dose-escalated group.

Acneiform skin toxicity is a class effect of all EGFR-targeting drugs currently in clinical use, including erlotinib for pancreatic and lung cancers and cetuximab and panitumumab for the treatment of metastatic colorectal and head-and-neck cancers.[2–4] Retrospective

analyses have shown a correlation between the grade of acneiform rash and the efficacy of anti-EGFR therapy – irrespective of the drug, underlying disease or whether the drug is given in combination with radiotherapy. For example, in colorectal cancer, the grade of acneiform rash is directly associated with the length of the observed survival.[5] In trials that investigated the efficacy of EGFR-targeting drugs in combination with chemotherapy, patients with colorectal cancer who did not experience any skin toxicity from the EGFR therapy had shorter survival periods than patients treated with chemotherapy alone. This correlation between rash and survival has been shown for erlotinib,[3] cetuximab and panitumumab.[4,5] However, the trials each showed an overall survival benefit for EGFR-targeting agents with chemotherapy over the chemotherapy alone arms, irrespective of skin rash. These benefits were significant for erlotinib in pancreatic cancer (P=0.03; HR 0.81)[3] and had a trend to significance in cetuximab (P=0.48; HR 0.91)[4] and panitumumab (P=0.072; HR 0.83).[5] Several host-related factors have been proposed to be predictive of the development of acneiform rash. Aside from the fact that younger male patients (<65 years) are more likely to develop acneiform rash,[3] molecular factors such as the single-sequence CA repeat intron-1 polymorphism of the EGFR also predict the likelihood of acneiform rash.

Acneiform rash is attributed to the direct inhibition of EGFR expressed in undifferentiated proliferating keratinocytes in the basal and suprabasal layers of the epidermis and outer layers of the hair follicle. This inhibition leads to premature keratinocyte differentiation and increased cell–cell attachment as well as reduced growth and migration, which collectively disrupt the formation of a normal, protective epidermal barrier. Indeed, Fracasso and colleagues revealed that elevated serum concentrations of cetuximab in patients receiving escalated cetuximab doses (with a maximum serum level reached at doses of 400 mg/m² per week) were accompanied by reduced EGFR protein expression in the skin compared with patients receiving the standard dose.[6] This decrease was already evident at a cetuximab dose of 250 mg/m² per week and there was a trend to even lower levels of EGFR expression in the 400 mg/m² cohort.[6] A separate study that focused on saturation of the EGFR with cetuximab in patients with head-and-neck tumours who were treated with cetuximab showed that EGFR saturation within the tumour was dose dependent; an initial cetuximab loading dose of 400 mg/m² followed by 250 mg/m² weekly achieved almost complete saturation of EGFR in the tumour tissue.[7] These data suggest that the acneiform rash reflects the saturation of EGFR in the tumour. Furthermore, the study demonstrated that a small number of patients might benefit from 400 mg/m² per week cetuximab in terms of downregulating EGFR in the skin – resulting in acneiform rash – and maximising EGFR saturation by cetuximab in the tumour.

> "...there was no obvious difference in haematological adverse events between patients receiving the standard dose and those receiving the elevated regimen"

An inflammatory response – including increased production of cytokines such granulocyte-macrophage colony-stimulating factor and recruitment of inflammatory cells – also contributes to the development of the characteristic rash.[8] This inflammatory response suggests that EGFR inhibition increases the recruitment of inflammatory cells involved in the immune response against the tumour. Such an immune reaction might further explain the correlation between the occurrence of acneiform rash and a superior outcome, which is observed irrespective of KRAS mutational status.[4] Although a correlation between acneiform grade and the inflammatory response inside the tumour in the presence of cetuximab therapy has not been shown, Tabernero and colleagues have demonstrated that downregulation of proteins downstream of EGFR – such as phosphorylated EGFR and phosphorylated MAPK – and upregulation of STAT3 (signal transducer and activator of transcription 3 protein) in the skin do occur in tumours treated with cetuximab in a dose-dependent manner.[9]

The efficacy of anti-EGFR drugs is also influenced by the presence of genetic alterations, which inhibit downstream pathway signalling. In colorectal cancer, in addition to KRAS codon 12 and 13 mutations, NRAS, BRAF (V600E), PI3KCA and AKT1 (E17K) mutations as well as expression of PTEN are associated with resistance to cetuximab. Furthermore, EGFR mutations and KRAS amplification were also noted to be associated with cetuximab resistance.[10] If the mechanism by which tumours are resistant to cetuximab therapy was inherited, dose escalation would not likely show benefit. However, patients without the genetic mutations that confer inherited resistance, and

Key point

Higher doses of cetuximab are well tolerated and lead to increased grade ≥2 acneiform rashes; we await the results from the prospective EVEREST II trial, which will test whether patients with increased acneiform rash have longer overall survival.

whose tumours do not show complete EGFR saturation when receiving standard doses of cetuximab, might benefit from escalated cetuximab doses. Those higher doses might further downregulate EGFR expression in the skin and, therefore, the patients might develop a higher grade of acneiform rash.

As almost 90% of patients treated with cetuximab display some grade of acneiform rash, the therapeutic window of cetuximab dose escalation might be narrow. Although the small size of the EVEREST trial limits the conclusions we can draw, these preliminary data warrant further studies. We await the data of the prospective EVEREST II trial before we can consider the clinical implications of the concept of escalating cetuximab guided by the clinical parameter of acneiform rash.

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Competing interests

Sebastian Stintzing declares associations with Amgen, Merck KGaA and Roche. Heinz-Josef Lenz declares an association with Merck KGaA. See the original article online for full details of the relationships.