

Controversial issues in managing locally advanced head and neck cancers

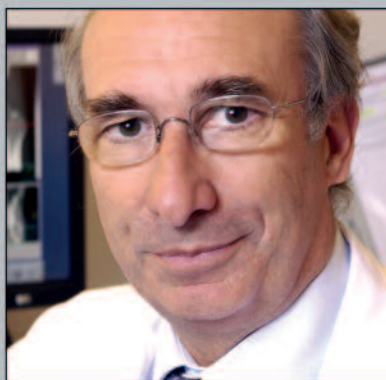
Great strides have been made in managing patients with locally advanced squamous cell cancer of the head and neck over the past 20 years. Novel approaches using chemoradiation (CRT) have improved disease control and quality of life. But controversies remain about how to optimise the use of CRT, including the role for targeted therapies, and how best to manage high-risk patients.

Major developments in managing patients with locally advanced squamous cell carcinomas of the head and neck have led, in many clinical settings, to significant advances in treatment efficacy and improvements in disease prognosis. The co-administration of chemotherapy and radiotherapy – chemoradiotherapy – both as definitive and adjuvant treatment, has been shown to be more efficacious than radiotherapy alone. However, recent prospective trials warn that poor tolerability with aggressive approaches impacts on treatment dose intensity, leading to the delivery of sub-optimal regimens.

Tailoring novel, multidisciplinary approaches based on drug–radiation interactions enables clinicians to optimise treatment outcomes in terms of both disease control and quality of life. As therapy becomes more intense, it is essential to monitor treatment-related morbidity as a crucial element in estimating the

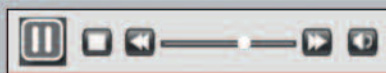


European School of Oncology e-grandround



The European School of Oncology now presents weekly e-grandrounds which offer participants the opportunity to discuss a range of cutting-edge issues, from controversial areas and the latest scientific developments to challenging clinical cases, with leading European experts in the field. One of these will be selected for publication in each issue of *Cancer World*.

In this e-grandround, Jacques Bernier, Department of Radio-oncology, Genolier Swiss Medical Network, Genolier, Switzerland, reviews the controversies in managing locally advanced head and neck cancers. His presentation was summarised by Susan Mayor.



The recorded version of this and other e-grandrounds, including the discussion following the presentations, can be accessed at <http://tiny.cc/grandround>

therapeutic gain from different strategies. The increasing use of longer, more aggressive combined treatments provokes a number of controversies regarding the impact on disease control, both above the clavicle and distantly, and the potential deleterious effect on adherence with radiotherapy and systemic treatment doses.

The focus of this e-grandround is on three main aspects of head and neck oncology: organ preservation, the treatment of unresectable disease and management in the postoperative setting.

Recent data for 2002 show that there were more than 500,000 new cases of squamous cell carcinoma of the head and neck (SCCHN) worldwide, and 300,000 deaths. Of these, just under half (42%) affected the oral cavity as the primary tumour site, one-third (33%) the larynx, and one-quarter (25%) the pharynx. Altogether, these cancers account for approximately 5% of all malignancies worldwide. This excludes cancers of the nasopharynx, which are more frequent in Asian countries.

Studies have demonstrated that chemoradiation (CRT) is more effective than radiotherapy alone in the treatment of locally advanced SCCHN. However, use of CRT is associated with a significant increase in acute toxicity. The maximum tolerable toxicity may have been reached with the dose intensities currently used.

The Meta-analysis of Chemotherapy in Head and Neck Cancer (MACHNC), which is probably the most well-known study in this area, showed that the addition

of chemotherapy to radiotherapy achieves benefits in locoregional control and in overall survival. Results showed that concomitant CRT was more effective than use of adjuvant or neoadjuvant treatment with radiotherapy alone, with a gain in survival of 19%, which is highly significant.

Does this mean that CRT should be given to all patients with locally advanced disease? Certainly not, we need to consider the individual patient. A recent substudy showed that age should be taken into account.

Stratifying the gain in overall survival with CRT versus age showed a gradual decrease in benefit between the ages of 50 and 70 years, with a minimal gain for patients aged 70 and older. This is something that should be considered at the time of making treatment decisions, and emphasises the need for individual patient decision-making on a case-by-case basis.

The other side of the coin is toxicity. This was certainly illustrated in a study by Cooper et al., demonstrating that the use of CRT in the postoperative setting results in a significant increase in acute toxicity – both nonhaematological and haematological – compared to radiotherapy alone (*N Engl J Med* 204:1937–44). More than three-quarters (77%) of patients treated with CRT had toxicity of grade 3 or more compared to 34% of those who had radiotherapy alone ($P<0.001$) following surgery. This demonstrates that there is a price to pay for patients given chemotherapy concomitant with radiotherapy.

TOO TOXIC?

Is the therapeutic index for CRT jeopardised by its toxicity? The answer to this question can be gained by looking at three randomised phase III trials, carried out in France, Switzerland and Germany.

Results showed that use of CRT compromised patients' adherence to chemotherapy, and this loss of adherence increased with the number of chemotherapy cycles. Approximately one-third of all patients did not receive the intended number of chemotherapy cycles (*J Clin Oncol* 22:4665–73, *JNCI* 91:2081–86, *J Clin Oncol* 16:1318–24).

There are two main observations regarding the future of CRT, at least with the drugs currently in use. The first consideration is that the acute toxicity of CRT compromises adherence to chemotherapy and radiotherapy protocols in more than one-third of cases. As a consequence, these patients receive suboptimal doses (or dose intensities) of chemotherapy and/or radiotherapy. The second issue is the late effects of CRT.

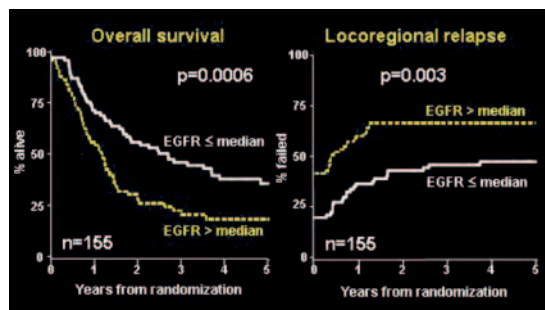
A study by Argiris et al. provides valuable information on these issues (*Clin Cancer Res* 10:1956–62). Results from five studies which investigated the role of CRT in locally advanced disease showed that disease progression and comorbidities were the two main causes of death following therapy. However, treatment-related causes were in third position, accounting for 15% of deaths, with 9% being early deaths and 6% late deaths due to complications associated with treatment.

So, both acute and late effects of CRT on normal tissue are a matter of concern. These concerns, together with recent advances in translational research with noncytotoxic agents, have led teams to embark on research along new avenues with targeted therapies.

The main controversies

- Is the therapeutic index for chemoradiation jeopardised by its toxicity?
- Do we know how best to exploit targeted therapies?
- How aggressive should we be with adjuvant treatments?
- Should we use chemoradiation or sequential treatment in high-risk patients?

EGFR: A MARKER FOR RESPONSE



Higher EGFR expression is associated with a higher risk of relapse and poorer survival following radiation therapy

Source: K Ang et al. *Cancer Res* 62:7350–56

ARE TARGETED DRUGS THE ANSWER?

Can we opt for other ways of treating patients that could increase the therapeutic index, using targeted therapies? Research began two decades ago in developing molecular therapies and strategies that act on specific proteins, processes and pathways implicated in cancer. The rationale for the targeted approach is to increase selectivity for tumour cells and reduce toxicity in normal tissues. This discussion will focus on the interaction between radiotherapy and antibodies against epidermal growth factor receptor (EGFR).

EGFR is a member of an important family of transmembrane proteins associated with signalling pathways central to cell growth and differentiation. When a specific ligand binds to the EGFR, the receptor activates a number of signalling pathways, in particular AKT, STAT and MAPK. This results in gene transcription in the cell cycle progression, affecting proliferation/maturation, survival and anti-apoptosis, angiogenesis and invasion/metastasis. Blocking the EGF receptor is likely to affect tumour cell growth and response to treatment.

A lot of things changed after the

study a few years ago by Ang et al. (*Cancer Res* 62:7350–56), which showed the predictive value of EGFR expression as a marker for response to radiotherapy. The study demonstrated a strong correlation between EGFR expression and treatment outcome in a subgroup of 155 patients. Whatever the endpoint – overall survival or locoregional relapse, the higher the EGFR expression, the more dismal the progression. How can we exploit this observation to optimise patient treatment?

Among the agents able to inhibit EGFR activation, cetuximab (C225) has been the most investigated so far. Cetuximab is an IgG1 monoclonal antibody that binds specifically to EGF receptors and inhibits endogenous ligand binding, thereby blocking receptor dimerisation; tyrosine kinase phosphorylation and receptor-dependent downstream signalling in the cytosol.

One of the first translational, *in vitro* studies with cetuximab (*Cancer Res* 53:4637–42) demonstrated marked synergy with cisplatin in A431 xenograft growth inhibition. The addition of C225 to cisplatin induced complete inhibition of cell growth. A few years later, a further study demonstrated the same pattern with C225 when added to radiotherapy.

The translational research studies set the stage for prospective clinical investigations with cetuximab plus radiotherapy. A study by Bonner et al. (*N Engl J Med* 354:567–578) assessed radiotherapy plus cetuximab in patients with squamous-cell

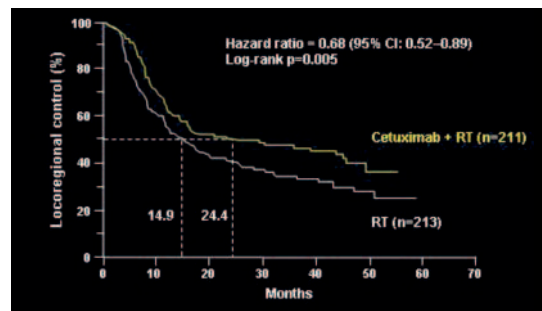
carcinomas of the head and neck. The majority of the patients presented with pharynx cancer, with the tumours arising mostly from the oropharynx (63%). About one-quarter of the patients had larynx tumours.

Patients were stratified by TNM stages, performance status and radiation schedule. The control arm received radiotherapy alone, either in conventional or accelerated regimens, while the experimental arm was given the same regimen of radiotherapy together with weekly doses of cetuximab, with an initial dose just before the start of radiotherapy. The study accrued 424 patients.

The main endpoint was locoregional control. This increased from a median of 14.9 months to 24.4 months with cetuximab (log rank $P=0.005$). The locoregional control rate at three years was 13% higher in favour of the cetuximab arm (47% vs 34%), which was highly significant ($P<0.01$). The same pattern was seen for overall survival, with a difference of almost 20 months for the combined modality over radiation alone, and a survival rate difference of 10% at three years (55% vs 45%; $P=0.05$).

The safety profile is worth revisiting. There was no difference in radiation-

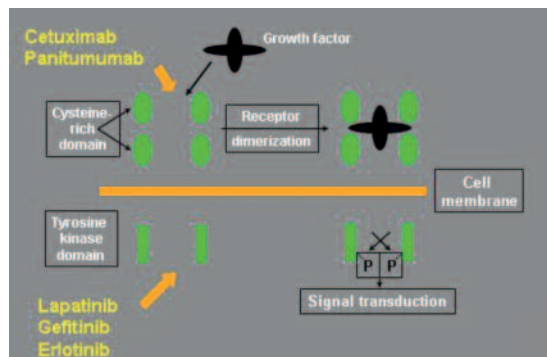
BENEFIT OF CETUXIMAB



Adding the EGFR inhibitor cetuximab to radiotherapy improves locoregional control

Source: J Bonner et al. *N Engl J Med* 354:567–578

HOW EGFR INHIBITORS WORK



EGFR is a protein associated with signalling pathways central to cell growth and differentiation. Blocking the EGF receptor is likely to affect tumour cell growth and response to treatment

induced toxicity when cetuximab was added to radiotherapy. As expected, the only difference observed was an acne-like rash, which was observed in 17% of the patients with grade 3–5 side-effects treated with cetuximab, compared to only 1% of those given radiotherapy alone. Infusion-related reactions were seen in only 3% of the cetuximab-treated group, due to a hypersensitivity to the infusion.

How does chemoradiation compare with cetuximab plus radiotherapy? As discussed previously, three trials showed a significant decrease in adherence to CRT, with two-thirds of patients able to complete two cycles of chemotherapy. Bonner demonstrated adherence of about 90% with cetuximab plus radiotherapy, so it seems that adherence is better with a protocol based on targeted therapy.

A survival advantage has been demonstrated with both modalities. Four trials of CRT showed a median survival advantage of 7–18 months, while the survival advantage in the Bonner trial was 20 months.

Targeted therapies certainly work in head and neck cancer, and there are now

several options. First, there are agents that act on the outer domain of the EGFR, including cetuximab and panitumumab. Second, there are the small molecules, such as lapatinib, gefitinib and erlotinib, which inhibit the tyrosine kinase domain at the first level of the phosphorylation mechanism.

The Bonner trial demonstrated that cetuximab plus radiotherapy is more efficacious than radiotherapy alone. It compares favourably with CRT in terms of efficacy and is less toxic. Several ongoing studies are investigating the role of CRT plus cetuximab.

SELECTING PATIENTS

Should chemotherapy be added to radiotherapy in all high-risk patients? To try to answer this question, it is useful to go back to the design of the EORTC 22931 study, which was conducted in the 1990s. After primary surgery, patients were randomised to receive either postoperative radiation therapy with a conventional regimen or to postoperative radiotherapy with the same regimen plus chemotherapy with cisplatin (DDP) at a dose of 100 mg/m² on days 1, 22 and 43.

One of the most striking results was the increase in overall survival with CRT. The Kaplan Meier curves showed a significant increase with CRT, with a difference of 13% in overall survival at five years (P=0.01).

At the same time, the RTOG team (Radiation Therapy Oncology Group) conducted a similar trial with the same design, also in patients

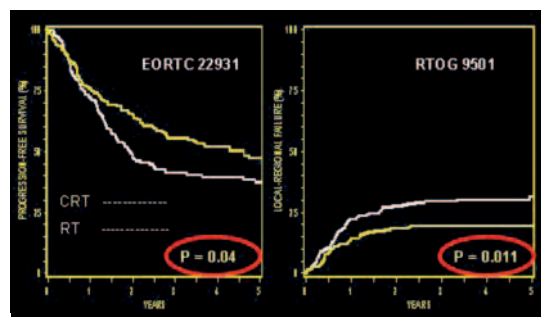
presenting with locally advanced disease. The primary endpoints in both studies – progression-free survival in the EORTC study, and local-regional failure in the RTOG study – showed that CRT was superior to radiotherapy alone.

What is noteworthy in these trials is that, when we deal with locally advanced disease, the selection criteria can be very different from one study to another. In the EORTC study, stage III-IV disease, oropharynx or oral cavity tumours with level 4 or 5 lymph nodes, perineural disease and vascular embolisms were considered high-risk factors.

In contrast, the RTOG study identified two or more positive nodes as indicating high risk. The two studies identified only two high-risk factors in common – positive margins and extracapsular effraction (ECE). These two risk factors were associated with significantly poorer overall survival than the other risk factors in both studies.

Comparing the effect of chemotherapy in the two trials, there was a trend in favour of chemotherapy for patients without positive margins or ECE in the EORTC trial, but the RTOG study ▶▶

BENEFIT OF CHEMORADIATION



The two major trials showed better outcomes for chemoradiation compared with radiotherapy alone in both locoregional control and progression-free survival

Sources: J Bernier et al. *N Engl J Med* 350:1945–52; JS Cooper et al. *N Engl J Med* 350:1937–44



Ahmad Awada (AA), from the Institut Jules Bordet, Brussels, put questions to Jacques Bernier (JB) about the controversies surrounding CRT in head and neck cancers



AA: Do we need a study to compare chemotherapy directly with radiotherapy plus cetuximab?

JB: There is no direct and randomised comparison between radiotherapy plus targeted therapies versus CRT. This should be addressed. In terms of the recent past, it is useful to compare the study from Bonner demonstrating high efficacy and low acute toxicity (it is still a bit early to see late toxicity) with another study of CRT. Historical comparison shows the efficacy of cetuximab plus radiotherapy compares favourably with CRT and is less toxic – but there is no direct comparison.

AA: It is not clear what effect radiotherapy plus cetuximab might have on distant metastases – this is still a problem with concurrent chemotherapy and radiotherapy.

JB: CRT trials – both individual studies and intergroup studies – show it is very difficult to elicit benefit in terms of reduction of distant metastases with standard CRT. One study showed a small benefit in terms of the pool of CRT trials, but this is difficult to demonstrate on a large scale. We need other solutions to reduce distant metastases beyond the concept of CRT.

There are three options: a trial with induction chemotherapy – this is probably one solution, especially with taxotere plus cisplatin and 5-FU. The second option is to wait for results from sequential treatment – induction chemotherapy then CRT – looking at distant metastases and toxicity. The third option, as in EXTREME, is to include a maintenance trial with cetuximab or other targeted therapies in the long term. We observed survival benefit in EXTREME.

A combination of induction chemotherapy plus targeted therapy could be of interest to improve response rate. The EXTREME study showed improved

survival and response rate. We have to wait for results from two EORTC studies.

AA: In locally advanced stage III and IV head and neck cancers, there are now several strategies based on clinical trials. We have induction therapy followed by CRT and radiotherapy plus targeted therapy. I think we are in a better position to choose the optimal therapy for each patient.

JB: I agree. There is preparatory work to be done before deciding how to treat an individual patient. One aspect is to check the risk level – don't treat intermediate-risk patients in the same way as high-risk patients. Second, check the patient's general condition to assess whether he is sufficiently fit for chemotherapy. Third, check whether you are embarking on an organ preservation programme – whether you are aiming to keep a functional organ, e.g. the larynx, in place. Delayed toxicity must also be taken into consideration. Check all this before making a decision.

It is clear that, for low- and intermediate-risk patients, the toxicity of chemotherapy in combination with radiotherapy is not justified, so we need other solutions. From Bonner, targeted therapy plus radiotherapy is one solution. Hyperfractionation, or altered fractionation, can be used, with or without targeted therapy.

In very-high-risk patients, treatment depends on the general condition of the patient. There are probably two options. Induction chemotherapy can be used first in very bulky disease, difficult to irradiate disease, or patients at high risk and with distant metastases or bulky disease in the hypopharynx. An extreme risk level justifies differences in therapeutic approach.

AA: It is important to look at comorbidities. The aim of organ preservation and life expectancy could influence choice of therapy.

The Bonner study told us that a combination of radiotherapy plus cetuximab may be useful in patients with renal problems – chemotherapy is difficult in this group. This combination is useful because you could not give cisplatin. It also seems from the presentation that CRT is not really favoured in elderly patients. Here, might radiotherapy plus cetuximab be of interest?

JB: The effect of chemotherapy decreases with age; this is also found with hyperfractionation and altered fractionation without chemotherapy. With or without chemotherapy, there is a decrease in effect with age, probably due to dose intensity with radiotherapy alone or radiotherapy plus chemotherapy not having a very positive effect above the age of 70. There is definitely a place for other solutions – a test use of targeted therapy plus radiotherapy in a subset with a lot of comorbidities is fully justified.

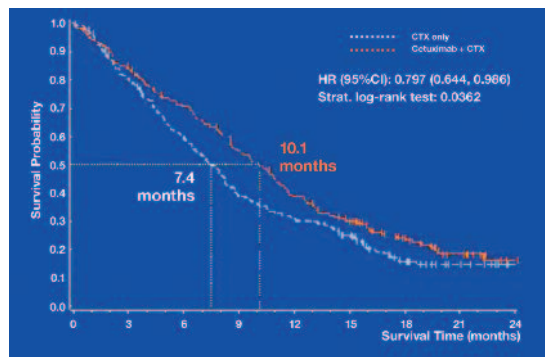
AA: Any contraindication to cetuximab with antabuse (disulfiram)? To my knowledge, there is no information on this.

JB: I have not seen any notification on potential interaction between the two compounds.

AA: Is there any role for electroporation therapy [designed to increase uptake of a therapeutic agent into the cell interior] in combination with targeted therapy?

JB: No, it may apply for some oral cavity or oropharynx tumours, as it is quite active but quite toxic to the mucosa. It is still experimental, with no large-scale study. The toxicity of this method is rather high, so to combine it with other toxic drugs could be a problem. Images I have seen after electroporation suggest that you should use it with caution, but it could be very efficient for small lesions.

IMPACT ON METASTATIC DISEASE



Last year, the EXTREME trial demonstrated an increase in overall survival in patients with advanced disease from 7.4 to 10.1 months by adding cetuximab as a maintenance therapy to chemotherapy – this was the first increase in 20 years

Source: J Vermorken, presentation at ASCO 2007

demonstrated no effect of the addition of chemotherapy.

In terms of the postoperative setting, differences in selection criteria explain variations in the impact of chemotherapy. High-risk patients derive a benefit from CRT compared to radiation alone in the postoperative setting. Adjuvant CRT and radiotherapy are particularly indicated for patients with positive surgical margins and those with ECE in neck nodes.

CRT OR SEQUENTIAL TREATMENT?

The use of chemotherapy followed by radiotherapy was investigated 15 years ago, when an EORTC study compared it to primary surgery. More recently, two trials, one in Europe and one in the US, investigated the impact of the addition of docetaxel and cisplatin and 5-FU.

The EORTC study 24971 included patients with unresectable SCCHN, who were treated with four cycles of induction chemotherapy with PF (cisplatin plus 5-FU) as standard treatment, with the addition of docetaxel in the

experimental arm. This trial demonstrated significant benefit in terms of overall survival in patients treated with docetaxel plus cisplatin and 5-FU (TPF).

Several institutions have been investigating the use of sequential treatments, for which the rationale is:

1. to decrease numbers of failures above the clavicle, which is bound to result from high response rates and enhanced complete response rates prior to CRT;
2. to reduce the incidence of distant metastases, which is bound to result from the use of full doses of chemotherapy, especially during the induction phase.

Sequential treatment studies have used different regimens of induction chemotherapy, such as PF/TPF every three weeks x 3, or carboplatin/paclitaxel (C/P) every three weeks x 2, followed by concomitant CRT.

Use of a sequential treatment strategy has two main challenges. First, to achieve the objectives of fewer local and distant failures, sequential treatments must use aggressive induction therapy, which should not compromise the CRT dose intensity. Second, the integration of induction chemotherapy and CRT is likely to cause problems of tolerability, resulting in suboptimal treatment delivery, increased toxicity and reduced quality of life.

THE EXTREME TRIAL

It is worth mentioning a trial conducted in another setting (patients with recurrent/metastatic SCCHN), which could provide new insight regarding the impact of systemic treatments on metastatic disease.

The EXTREME trial compared

chemotherapy with carboplatin or cisplatin and 5-FU versus the same regimen to which cetuximab was added. In the cetuximab arm, cetuximab was continued as maintenance therapy after a maximum of six chemotherapy cycles and compared to no maintenance treatment in the standard treatment arm.

Results, presented at ASCO in 2007, showed an increase in overall survival – for the first time in 20 years – from 7.4 to 10.1 months. This gives new insight, showing what we could expect from maintenance treatment, with a positive impact on distant metastases, which remain a growing problem with the improvements in locoregional control of locally advanced disease.

CONCLUSIONS

The high levels of toxicity associated with chemotherapy are not justified in patients with low rates of failure above the clavicle.

The main options are:

- Radiotherapy plus targeted therapies (EGFR inhibitors, VEGF inhibitors etc)
- Definitive radiotherapy, with altered fractionation
- In the postoperative setting, the use of molecular markers as prognostic indicators for treatment outcome

In high-risk patients, chemoradiation is more efficacious than radiotherapy alone, but is more toxic. At the moment, there has been no direct comparison between chemoradiation and radiotherapy plus targeted therapies.

Current approaches might be improved by increasing local control obtained by radiotherapy through use of novel cytostatic agents, combining cytotoxic and non-cytotoxic agents and use of peri-operative chemotherapy in the adjuvant setting.

Options to reduce the risk of distant metastases include novel multidrug regimens and maintenance treatment with chemotherapy or targeted agents.