Efforts to improve the efficacy of treatment for SCCHN have led to the use of multimodality approaches with combinations of surgery, radiotherapy and chemotherapy. Conventional head and neck radiotherapy, a standard approach for locoregionally advanced disease, is associated with a variety of well-known acute and long-term toxicities. These chronic toxicities (i.e. xerostomia, dysphagia, fibrosis) can impact negatively on patient quality of life. Altered radiation fractionation regimens that incorporate acceleration and/or hyperfractionation can improve locoregional control but also increase acute toxicities for head and neck cancer patients. Intensity modulated radiation therapy (IMRT) has emerged as a promising method for delivering effective radiation dose to head and neck tumour targets while reducing exposure of surrounding healthy tissue. Another method for improving head and neck cancer outcome with conventional radiotherapy is with the concurrent addition of chemotherapy. Indeed, chemoradiotherapy is now a standard treatment approach for locoregionally advanced disease. Molecular targeted agents, such as the epidermal growth factor receptor (EGFR) antagonist, cetuximab (Erbitux®), have recently been shown to enhance the effects of radiotherapy, and reports to date suggest that this potentiation occurs without an increase in the characteristic toxicities associated with head and neck radiation.

Key words: cetuximab, EGFR, head and neck cancer, radiation, radiotherapy

Introduction

External beam radiation therapy has long been a cornerstone of therapy for early stage and locoregionally advanced head and neck cancer. In general, ‘conventional radiotherapy’ involves the delivery of fractionated radiation (commonly 2 Gy daily to 70 Gy) and is complicated by the close proximity of tumour and normal tissue structures such as the spinal cord, brain stem, parotid glands and optic pathway structures. With conventional head and neck radiotherapy, masking techniques and routine laser alignment, daily set-up variations of 3–6 mm are common. To allow for these variations, and for uncertainties in tumour definition, generous safety margins are used. While this approach helps to ensure irradiation of all malignant tissue, it also subjects healthy tissue to full dose radiation exposure and the recognized side effects of treatment. Radiation mucositis with associated pain is experienced by virtually all patients [1] (Figure 1), and can last for 3–8 weeks following treatment. Chronic radiation toxicities, including mucosal fibrosis and atrophy, xerostomia, dental decay, soft tissue necrosis, osteonecrosis and taste disturbances (dysgeusia, ageusia), can occur in many patients. Not only can these effects compromise optimal treatment delivery, they can lead to a lifetime risk of oral sequelae with profound effects on patient quality of life [2].

Altered radiation fractionation

Attempts to improve on both the efficacy and toxicity profile for head and neck radiotherapy led to the development of a number of alternative delivery schedules, employing different fractionation regimens [3, 4]. Two dominant altered fractionation themes include: accelerated fractionation and hyperfractionation. Accelerated fractionation involves a reduction in overall treatment time, with (hybrid) or without (pure) change in fraction size and total dose. Acceleration is based on the premise that the reduced overall treatment time reduces the opportunity for tumour cell regeneration. The reduction in overall treatment time, however, can influence the response of healthy tissue and will lead to an increase in acute side effects. Hyperfractionation involves the use of multiple smaller dose fractions (<2 Gy) delivered at an increased frequency (commonly twice daily), affording an increase in the total dose delivered over the same time as conventional radiotherapy, but with equivalent long-term toxicities. Once again, the acute toxicity profile is generally increased.

Altered fractionation has been shown to provide improved locoregional control in a number of head and neck cancer studies. However, improvements in overall survival have generally been modest. In a classic trial of radiation acceleration in Denmark, 1476 patients were randomized to either five or six fractions per week (2 Gy daily) to the same total dose (66–68 Gy in 33–34 fractions in most cases) [5]. The accelerated 6 days per week regimen led to a significant increase in overall 5-year locoregional control rates (70% vs. 60%, \( P = 0.0005 \)) and voice preservation among patients with laryngeal cancer (80% vs. 68%).
amifostine treatment. A very accelerated head and neck radiation delivery regimen reduced the severity and duration of mucositis associated with reported that amifostine administered prior to radiation re- size and total dose are made [5, 6, 9]. Bourhis et al. (2000) not lead to increased late effects if strict attention to fraction schedules will increase the incidence of acute toxicities but will

Figure 1. Confluent grade III radiation-induced mucositis in a patient undergoing intensified radiation fractionation for advanced oropharyngeal cancer.

$P = 0.007$). There was also a significant improvement in disease-specific survival (73% vs. 66% for six vs five fractions, $P = 0.01$) but not in overall survival. The four-arm altered fractionation randomized Radiation Therapy Oncology Group (RTOG) trial showed that patients treated with hyperfractionation and accelerated fractionation with concomitant boost had significantly better locoregional control ($P = 0.045$ and $P = 0.050$ respectively) than those treated with standard once-daily fractionation [6]. There was, however, no significant improvement in overall survival. Interestingly, Khalil and colleagues suggest that interpretation of results from randomized trials of altered fractionation radiation therapy can be complicated by variations in treatment compliance [7].

Altered fractionation has also shown potential efficacy in the post-operative setting for head and neck cancer. In one study, compared with conventional fractionation (60 Gy over 6 weeks, 2 Gy per fraction, treating 5 days per week), the use of accelerated hyperfractionation (46.2 Gy per 33 fractions [1.4 Gy per fraction] over 12 days, treating 6 days a week) led to a significantly improved 3-year locoregional control rate (88% vs 57%, $P = 0.01$) [8]. However, acute toxicity is enhanced and there was no significant difference in overall survival between the groups.

In terms of side effects, intensified fractionation schedules will increase the incidence of acute toxicities but will not lead to increased late effects if strict attention to fraction size and total dose are made [5, 6, 9]. Bourhis et al. (2000) reported that amifostine administered prior to radiation reduced the severity and duration of mucositis associated with a very accelerated head and neck radiation delivery regimen [10], although more than one-third of patients did not tolerate amifostine treatment.

**Intensity-modulated radiation therapy**

One of the more recent adaptations of radiotherapy involves the use of intensity-modulated radiation therapy (IMRT) [11]. In IMRT, multiple shaped radiation beams are modulated to produce highly conformal dose distributions [12]. This approach enables the delivery of increased doses to tumour tissue while limiting the dose delivered to defined normal structures such as the salivary glands, auditory and optic apparatus, spinal cord and larynx. Figure 2 shows the parotid-sparing effects of IMRT in a head and neck cancer patient undergoing treatment for oropharyngeal cancer. The use of IMRT in oropharyngeal cancers has been reported in a number of small studies of patients with advanced disease (Table 1) [13–16]. In these single-institution reports, overall locoregional control was excellent, 91% at two years and 87% at four years. These represent early reports, however, with heterogeneous patient cohorts and variable use of chemotherapy. The use of IMRT in earlier stage disease is being investigated in a trial conducted by the RTOG (trial 0022). Patients with stage T1-2, N0-1 oropharyngeal cancer will receive IMRT to a total dose of 66 Gy in 30 fractions (2.2 Gy/fraction) for gross disease and 54–60 Gy in 30 fractions (1.8 Gy/fraction) for sub-clinical disease. A boost of 4–6 Gy is allowed to gross disease. All institutions in this multicentre trial were subject to rigorous IMRT credentialing and assessment of test case IMRT techniques and planning. The potential quality of life benefits of this approach in head and neck cancer patients are obvious. However, a cautionary note should be sounded: there are limited mature clinical data sets to date and the interpretation of available data is complicated by the use of variable techniques. Maturation of clinical data regarding long-term efficacy and toxicity will help to place IMRT in the overall treatment spectrum. In addition, IMRT is a relatively complex technique to perform well and variations in daily set up can have an adverse impact on the success of treatment [17]. The optimal selection and delineation of target volumes (e.g. by functional imaging), the preferred fractionation for optimal efficacy, the integration of IMRT with other therapies, and the standardisation of IMRT techniques are all issues that warrant further study [18, 19]. Nevertheless, IMRT brings great promise in head and neck radiation therapy, and a survey of US radiation oncologists showed that the use of IMRT is increasing rapidly [20].

Valuable reports regarding toxicity profiles in head and neck IMRT are emerging. An evaluation of toxicity associated with IMRT in 126 patients, with a median follow-up of 38 months, showed grade 3/4 acute skin and mucosal toxicity in 32 and 52 patients, respectively, and grade 3 late effects (xerostomia and skin) in 1% and 2% of patients, respectively [21]. The precise, relevant and reproducible delineation of primary and secondary targets in head and neck cancer radiotherapy represents a major challenge. In this respect, the use of IMRT may be refined further by improving technical delivery. Currently, the most commonly used method involves delivery of radiation fields at fixed gantry angles using a multileaf collimator [22]. An emerging method of IMRT delivery involves tomotherapy, which combines radiotherapy and computed tomography to deliver beams from 360 degrees modulated by a multileaf collimator [22–24]. The improved imaging facility conferred by the CT enables targeted regions to be observed prior to, during and after treatment, allowing delivery of IMRT with even greater accuracy.
Chemoradiotherapy

Adding concurrent chemotherapy to radiotherapy (chemoradiotherapy) is now recognized to improve outcome in advanced head and neck cancer patients compared with once-daily radiotherapy alone and has become a standard approach for non-metastatic disease. Furthermore, the addition of chemotherapy to radiotherapy following surgery for resectable head and neck cancer with high-risk features shows improved locoregional control and disease-free survival [25, 26]. However, in both the definitive and post-operative head and neck setting, the enhanced survival outcome is accompanied by an increase in overall treatment toxicity profiles [25–27].

The potential outcome advantage for chemoradiotherapy in head and neck cancer patients has been further examined in several meta-analyses published between 1990 and 2001 [28–32]. Although the first meta-analysis revealed no tangible benefit associated with head and neck chemotherapy, the subsequent reports gradually identified small overall benefits accruing to patients treated with systemic chemotherapy. Indeed, the largest, most comprehensive meta-analysis to address the head and neck chemotherapy question (published in 2000) includes updated individual patient data [28]. This review included over 10 000 head and neck cancer patients from randomized trials between 1965–1993 and identified a small overall survival benefit (~4% at 2 and 5 years) for the use of chemotherapy. Subset analyses suggested no significant survival benefit for the use of neoadjuvant or adjuvant chemotherapy, but did suggest a benefit for the use of chemoradiotherapy. Since 1994, a series of relatively small but positive trials regarding chemoradiotherapy in head and neck cancer have been reported, suggesting that a successor meta-analysis (in progress) may be even more compelling in favour of chemoradiotherapy. Despite the small absolute survival gains, the recently reported results have led to the increasingly common use of chemoradiotherapy as a ‘standard of care’ for advanced head and neck cancer patients not receiving definitive surgery.

The randomized trials with chemoradiotherapy represent an important advance in head and neck cancer. Nevertheless, many questions remain unanswered, not least of which is the specific chemoradiotherapy schedule to recommend outside the context of controlled clinical trials. Some studies used once-daily radiation, others twice-daily radiation. Some studies used cisplatin or mitomycin alone, whereas others used 5-FU or carboplatin. The dose/delivery schedule of platinum varies dramatically from every 3 weeks (100 mg/m²) to low-dose daily (6 mg/m²)
administration. In addition, not all of the published randomized trials show a survival advantage for chemoradiotherapy over radiation alone. To date, there remains no clearly defined consensus for practitioners to embrace as a ‘standard’ chemoradiotherapy regimen for head and neck cancer. However, the most common global practice appears to include the administration of cisplatin concurrent with radiation, either low-dose weekly at 30–40 mg/m² or every 3 weeks, with doses of 75–100 mg/m². This would seem a reasonable approach taking into account all of the available data. Hopefully, this issue of ‘optimal’ treatment regimens will become better defined in the coming years through the completion and maturation of additional randomized trials.

Radiation combined with targeted therapies

The addition of molecular targeted therapies in head and neck cancer offers another potential method to further improve outcome. Recent years have seen a dramatic increase in interest in the use of targeted therapies and methods to maximize the clinical potential of these compounds are currently being explored.

Cetuximab is an IgG1 monoclonal antibody (MAB) that specifically targets the epidermal growth factor receptor (EGFR) with high affinity and competitively inhibits endogenous ligand binding [33]. The EGFR is central to the growth regulation of healthy tissues, and also plays an important role in tumorigenesis and the progression of malignant disease. As such, the EGFR is an important tumour target. As well as being expressed on the surface of healthy cells, the EGFR is commonly expressed at high levels in a variety of epithelial solid tumours, including SCCHN and colorectal cancer [34, 35]. EGFR expression by tumours is commonly associated with more aggressive disease and decreased survival [36, 37]. A study in SCCHN showed that the 5-year survival rate was 81% for patients with EGFR non-expressing tumours compared with 25% for patients with EGFR-expressing tumours \((P < 0.0001)\) [38].

The potential for cetuximab to modulate treatment outcome in SCCHN has been well developed in pre-clinical studies [39]. In culture studies, cetuximab induced G1 cell cycle arrest and enhanced the radiosensitivity of human SCC tumour cell lines [39, 40]. Augmentation of radioresponse in SCC tumour xenografts in athymic mice has also been established [39, 41]. The radiosensitising effects of cetuximab in the pre-clinical setting prompted its investigation in combination with radiotherapy in clinical studies in head and neck cancers [42, 43].

Cetuximab plus radiotherapy

In a phase I study, the combination of cetuximab plus simultaneous radiotherapy demonstrated high anti-tumour activity as first-line treatment in locoregionally advanced SCCHN [44]. Sixteen patients with advanced SCCHN received treatment with the combination of cetuximab and either conventional (70 Gy, 2 Gy/day) or hyperfractionated radiotherapy (76.8 Gy, 1.2 Gy/ twice daily). Treatment was generally well-tolerated and all patients achieved major objective response (13 complete and two partial responses). These results helped to support initiation of a phase III study to examine the combination of cetuximab with radiation in head and neck cancer.

At the 2004 annual meeting of the American Society of Clinical Oncology, preliminary findings were presented from the first large-scale trial to investigate the efficacy of adding cetuximab to radiotherapy for locoregionally advanced head and neck cancer patients. This international multicentre phase III study showed that the addition of cetuximab to high-dose radiotherapy significantly improved locoregional disease control and survival compared with radiotherapy alone in patients with locoregionally advanced SCCHN [45]. In this study, 424 patients were stratified by Karnofsky performance index (90–100% vs 60–80%), regional node involvement (no vs. yes), tumour stage (T1-3 vs T4) and radiation fractionation (concomitant boost vs. once-daily vs. twice-daily) and then randomized to treatment with radiation alone or in combination with cetuximab. Following completion of trial treatment, patients were followed up with radiographic imaging every 4 months for 2 years and then every 6 months for up to 5 years.

The median age of patients was 57 years and, as expected with head and neck cancers, 80% were male. Over two-thirds (69%) of patients had a KPS of 90–100%. The majority of patients presented with oropharyngeal tumours (60%), 25% had laryngeal tumours and 15% had hypopharyngeal tumours. The treatment arms were well-balanced with respect to patient and treatment characteristics. Patients were followed up for a median of 38 months.

The use of cetuximab prolonged overall survival, almost doubling the median survival from 28 months to 54 months \((P = 0.02)\) (Table 2). The two- and three-year survival rates of patients were 55% and 44% for those receiving radiotherapy alone, and 62% and 57% for those receiving radiotherapy and cetuximab.

The adverse event profile of patients receiving treatment was typical of that associated with high-dose radiotherapy for head and neck cancer, including mucositis/stomatitis, but also featured side effects associated with EGFR inhibitors and monoclonal antibodies. Approximately one-third (34%) of patients receiving cetuximab developed grade 3/4 skin reactions compared with 18% receiving radiotherapy alone \((P = 0.0003)\) (Table 3). These skin reactions were generally easily managed and reversible following treatment completion. Six patients (3%) who received cetuximab developed a grade 3/4 infusion reaction. Importantly, however, the use of cetuximab did not appear to exacerbate radiation-induced mucositis.

Table 2. Addition of cetuximab to radiation prolongs overall survival in patients with locally advanced SCCHN: results from a randomized phase III study [45]

<table>
<thead>
<tr>
<th>Survival</th>
<th>Radiation alone ((n = 213))</th>
<th>Cetuximab + radiation ((n = 211))</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median survival</td>
<td>28 months</td>
<td>54 months</td>
<td>0.02</td>
</tr>
<tr>
<td>Two-year survival</td>
<td>55%</td>
<td>62%</td>
<td>–</td>
</tr>
<tr>
<td>Three-year survival</td>
<td>44%</td>
<td>57%</td>
<td>–</td>
</tr>
</tbody>
</table>
The impact of cetuximab on neck dissection healing was evaluated in a sub-group of 115 patients enrolled from the four leading accrual centres where 39 neck dissections were performed following completion of treatment [46]. Twenty patients had received radiotherapy alone and 19 had received radiotherapy plus cetuximab. There was no difference in the average length of hospital stay following neck dissection (2.1 days vs 2.8 days, respectively) or in the average time until neck drain removal (3.3 days vs 3.1 days) between the two groups of patients, suggesting that cetuximab does not significantly affect wound healing following neck dissection as carried out in this trial.

Cetuximab plus chemoradiotherapy

The use of cetuximab in combination with chemoradiotherapy has also been investigated. Pfister and colleagues reported results of a study in which patients with locoregionally advanced SCCHN received a type of concomitant boost radiotherapy (1.8 Gy/day for weeks 1–4, then 1.8 Gy (am) and 1.6 Gy (pm) for weeks 5–6, for a total dose of 70 Gy), together with cisplatin (100 mg/m² IV, weeks 1–4) and cetuximab (initial dose 400 mg/m², followed by subsequent doses of 250 mg/m²/week) [47]. Surgery was reserved for cases of relapse or suspicion of persistent neck disease. A total of 21 patients, with a median age of 57 years and good performance status (median KPS 90%), entered the study. The majority of the patients (86%) had stage IV disease. The overall activity of this regimen was excellent. At a median follow-up of 26.1 months, 16/21 (76%) patients were disease-free, including five who underwent post-treatment neck dissections. However, there were significant toxicities observed in this study that prompted early closure. There were 10 grade 4 toxicities and two deaths on treatment (one due to pneumonia and one to unknown cause). Despite the serious toxicity, the clinical activity of this approach suggests that alternative chemoradiotherapy schedules may warrant evaluation.

A number of other EGFR inhibitors have shown activity against head and neck cancers, including the tyrosine kinase inhibitors, gefitinib and erlotinib. Gefitinib (500 mg/day) has demonstrated single-agent activity in patients with recurrent/metastatic disease, with a response rate of 11% [48]. A lower dose of gefitinib (250 mg) in this setting was associated with a reduced incidence of grade 3/4 toxicity, but also a reduced response rate (4%) [49]. Data from phase I and II studies show that erlotinib is active in pretreated recurrent/metastatic SCCHN both as a single agent [50] and in combination with docetaxel [51]. In terms of other EGFR-directed MABs, the humanized anti-EGFR MAb, h-R3, was shown to be tolerable when used in combination with radiotherapy in advanced head and neck cancers, and improved survival at higher doses of h-R3 was suggested [52]. Another MAb, ABX-EGF, a high-affinity, fully human IgG2 EGFR-targeted MAb, has shown single-agent activity in metastatic colorectal cancer [53]: mature data on its use in head and neck cancers are awaited. Recent pre-clinical studies in animals further suggest that combined treatment with cetuximab and erlotinib or gefitinib can augment the potency of EGFR signaling inhibition and tumour response [54, 55].

Conclusions

Stepwise improvements in head and neck cancer therapy are beginning to show favourable impact on this complex malignancy. Although the recent outcome improvements with altered radiation fractionation and chemoradiotherapy for advanced head and neck cancer patients appears quite real, the overall impact on the broad head and neck cancer population is modest, and the approaches are certainly toxic, complex and expensive to achieve. Head and neck cancer patients commonly carry excessive comorbidities in light of chronic alcohol and tobacco use, and they are also prone to the development of synchronous or metachronous upper aerodigestive tract malignancies. Many would not meet basic eligibility criteria for intensive chemoradiotherapy clinical trials. Indeed, very few randomized trials in head and neck cancer have enrolled more than 500 patients, reflecting the challenge of completing large scale trials in this cancer population. Improved precision and conformality of radiation dose delivery (e.g. IMRT) offers much promise for the reduction of long-term radiation toxicity in selected head and neck normal tissue structures (salivary gland, auditory apparatus, mandible, spinal cord). New molecular agents (such as cetuximab) which target growth factor receptors that appear central to growth for many head and neck cancers similarly offer promise to provide less toxic and more discriminate approaches for the future. For these new treatment strategies, as with the current generation of chemoradiotherapy studies, a rigorous, thorough and dispassionate evaluation of the overall impact of treatment on the welfare of the head and neck cancer patient population will be required.

Disclosure

The author holds research and consulting agreements with Genentech, Imclone and AstraZeneca.

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