Recent new approaches to the treatment of head and neck cancer

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Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer in the world and affects 50 000 Americans annually. During the past 20 years, treatments for HNSCC have changed dramatically due largely to the advent of novel approaches such as combined modality therapy, as well as improvements in surgical and radiotherapeutic techniques. Ongoing advances in the multidisciplinary management of this complex and multivariate disease process are resulting in improved function, quality of life and survival. Here, we review state-of-the-art therapy and presents selected advances in the treatment of head and neck cancer. ***Anti-Cancer Drugs*** **17:365–375 © 2006 Lippincott Williams & Wilkins.**

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Introduction

Head and neck squamous cell carcinoma (HNSCC) is the sixth most common cancer in the world and affects 50 000 Americans annually. Patients with HNSCC are at considerable risk of mortality, with more than 300 000 deaths attributable to the disease in 2000 [1]. Patients with locally advanced, operable HNSCC are known to be at high risk of treatment failure, ranging from locoregional recurrence to lymphatic spread to systemic dissemination. Attacking specifically each of these patterns of failure implies the use of a multimodal approach.

Diagnosis and staging

Nuclear medicine technologies continue to advance the diagnosis and staging of head and neck cancer. Positron emission tomography (PET) with fluorodeoxyglucose is already established for initial staging, particularly for the detection of metastatic disease [2]. PET has also been shown to be invaluable in the early follow-up of patients with advanced head and neck cancer. Whole-body PET scanning approximately 6 weeks after completion of a combined treatment regimen with radiation and chemotherapy can reliably identify locoregional residual cancer and distant metastases or secondary tumors in patients with advanced-stage HNSCC, and has a direct influence on management decisions [3].

Recent studies have demonstrated the potential for molecular imaging to go beyond current use in diagnosis and staging. Tumors treated with primary surgery were imaged pre-operatively with [^{99m}Tc]6-hydrazinonicotinic-labeled Annexin-V scintigraphy. Annexin-V binds selectively to apoptotic cells. Nuclear labeling enabled real-time in-vivo detection of apoptotic tumor cells as demonstrated by the correlation of scintigraphy with histologically determined apoptotic cells [4].

Multimodality care

Current management of locally advanced HNSCC has evolved from poorly effective single-modality therapy to an integrated, highly effective multidisciplinary approach. Unlike early-stage HNSCC, all three modalities – surgery, radiotherapy and chemotherapy – play vital and complementary roles. Current treatments used for locally advanced disease can be classified as summarized by Seiwert and Cohen [5]: (a) surgery followed by adjuvant chemoradiotherapy (CRT) (or radiation), (b) CRT upfront (with surgery as a salvage treatment) and (c) induction chemotherapy followed by (i) CRT or (ii) other primary treatment options (radiotherapy, surgery).

Surgery followed by adjuvant CRT (or radiation)

Aggressive surgical resection, with or without adjuvant CRT, is the cornerstone of treatment for early disease [6]. In many patients, the necessary surgery can be disfiguring and may also affect everyday functioning, including swallowing, eating, breathing and speech, with a profound impact on quality of life [7]. Predictors of recurrence after surgical resection include involved margins of resection, extranodal/extracapsular spread, perineural invasion and the presence of two or more involved regional lymph nodes [8–10]. Since locoregional failures remained the dominant problem, adjuvant locoregional therapies such as radiation and subsequently CRT were

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added, and adjuvant therapy is now considered standard of care for stage III/IV disease.

An important contribution to our understanding of post-operative radiotherapy came from Fletcher [11], who showed that, in combination with surgery, a dose of approximately 50 Gy is sufficient to eradicate malignant microfoci in 95% of the cases with uninvolved surgical margins. Although only retrospective data exists [12], there is a broad consensus since the 1980s that it increases survival and a randomized prospective trial would be unrealistic at this point. Still, even with adjuvant radiotherapy, in the presence of high-risk features, the risk of local recurrence (27–61%), distant metastasis (18–21%) and death (5-year survival rate 27–34%) remain unsatisfactorily high [13].

Another area of active study is the determination of the most effective and tolerable total dose, schedule and administration technique of radiation therapy. When compared with a baseline single, daily, 5-day/week scheduling to a total dose approximating 70 Gy, a number of approaches exist to increase the therapeutic index of radiation. Hyperfractionation (greater dose per day) and accelerated fractionation (same dose over a shorter schedule) are the main alternatives. By delivering higher doses over a shorter time, it is postulated that tumor repopulation, hypoxemia and, thus, generation of radioresistant clones is reduced [14]. Altered fractionation has been shown to provide improved locoregional control in a number of head and neck cancer studies [15].

Another approach to improving local control and therapeutic index is to increase total tumor radiotherapy by methods such as stereotactic delivery and intensity-modulated radiation therapy. This approach enables the delivery of increased doses to tumor tissue, while limiting the dose delivered to defined normal structures such as the salivary glands, optic apparatus, spinal cord and larynx [15]. The dose–effect relationship appears complex and is probably influenced by confounding factors, the nature of which remain unknown. Suffice it to say that practical factors limit the intensification of treatment solely by altering radiotherapy to a degree that other ways of improving treatment are likely needed [16–18].

The first suggestions that chemotherapy could help improve outcome came from patients who had inoperable or metastatic tumors [19]. Post-operative CRT offers an approach that could enhance local control with radiosensitizing chemotherapeutic agents.

Several studies have suggested that concurrent CRT is a highly effective therapy for locally advanced HNSCC including tumors that are not amenable to surgery [20–22], justifying trials of concurrent CRT as post-operative (adjuvant) treatment.

The first trial to suggest a marked benefit of post-operative CRT over radiation alone in patients with high-risk features was a small trial by Bachaud *et al.* in 1996 [23]. In 2004, level I evidence was established with the publication of the results of two large-scale, independent, but similar, trials conducted in Europe and the US. Both studies demonstrated that, compared with post-operative radiation alone, adjuvant concurrent CRT (high-dose cisplatin and irradiation) given concomitantly was more efficacious in terms of locoregional control and disease-free survival [24,25]. With the publication of these two trials, the evidence demonstrating the potential value of concurrent post-operative CRT in high-risk operable HNSCC is strong.

For patients without high-risk features, the evidence of a benefit of CRT over radiation alone is less clear, with no randomized trials addressing this question. Additional studies and comparative analysis of the selection criteria and treatment outcomes across these two trials will be needed to gain a more accurate assessment of benefit and risk levels in specific patients. The role of concurrent CRT in the adjuvant setting of high-risk disease has now been established and validated. The best concomitant CRT regimens still need to be determined, although cisplatin-based chemotherapy is the current standard [19].

The optimal time frame to start adjuvant treatment post-surgery has not been studied sufficiently. Limited evidence and clinical experience with the time needed for patients to recover suggest that it should be within 4–6 weeks post-surgery [5]. More attention should be paid to the latency between the surgical procedure and the onset of radiotherapy or CRT. Too often, either organizational constraints or delayed wound healing postpone the start of adjuvant treatment beyond 6–7 weeks. Increased concentrations of growth factors during the healing period might account for the acceleration of tumor cell repopulation during a long post-operative latency period. Very few studies have however, taken this parameter into consideration [19].

CRT upfront (with surgery as a salvage treatment)

During the past decade, an attractive alternative to initial surgery has evolved. Originally pioneered for inoperable patients, upfront concomitant CRT has emerged as a definitive treatment option comparable to upfront surgical management in resectable patients.

Given its advantage with regard to organ preservation, and excellent reported local control and survival rates, CRT is increasingly used and has become the dominant treatment modality in many centers [26]. Concomitant CRT attempts to capitalize on radiosensitizing properties while delivering systemically active agents.

Consistently, CRT trials report an increased incidence of grade 3 and 4 acute toxicities, with mucositis and dermatitis being the most prominent. Severe long-term side-effects are however, not increased in comparison to radiation alone and virtually all patients recover from the intense treatment. Treatment should be preferentially performed at experienced centers that have an appropriate support infrastructure [27].

Multiple phase II trials using intensive CRT regimens have shown long-term survival rates of 60–70%, without surgery, for locally advanced HNSCC [22,28]. Based on suggestive phase II evidence, recent trials frequently now investigate combination chemotherapy. Commonly used agents include cisplatin, 5-fluorouracil (5-FU), taxanes, hydroxyurea and gemcitabine [22,29]. Recently, Adelstein *et al.* [21] showed that the addition of cisplatin to radiotherapy significantly improves survival over radiotherapy alone, with a projected 3-year survival of 37% compared with 23%. The toxicities of chemotherapy and radiotherapy are however, likely to be greater than with radiotherapy alone and impact severely on quality of life [30].

Even though some controversy remains, there is an increasingly better defined role for surgical management of certain patients after CRT. Cervical lymph node dissection even after a complete response to CRT is appropriate in patients with N2–N3 disease to optimize locoregional disease control [31,32]. The decision between upfront surgery followed by CRT compared with upfront CRT with the option of salvage surgery remains controversial. No adequate randomized trial has examined this question, and given inherent biases in patient selection and ability to stage patients in a comparable fashion, it is unlikely that we will have a definitive answer in the near future. Both approaches work well, can coexist, and allow matching of treatments to a patient's disease and preferences.

Induction chemotherapy followed by CRT or other primary treatment options

The administration of induction chemotherapy prior to definitive local therapy remains controversial. In addition to better control of locoregional disease, chemotherapy should prevent the subsequent appearance of metastases by eradicating occult metastatic deposits. Since distant metastases are now the cause of failure in 29% of patients with stage III/IV HNSCC, high-dose bolus chemotherapy, at least in theory, is more likely to achieve this objective, since the gain from a pure radiosensitizing effect of a low-dose cytotoxic agent is limited by the competing risk of distant failure [19].

Two European studies have shown evidence of a survival benefit with induction chemotherapy: the Italian Gruppo di Studio sui Tumori della Testa (GSTTC) study [33], which demonstrated increased cure rates in a subset of non-operable patients, and the French Groupe d'Etude des Tumeurs de la Tete et du Cou (GETTEC) trial, which was closed early [34]. The combination of induction chemotherapy and concomitant CRT appears to be of particular interest due to their complementary effects, with the former leading to a reduction of distant disease and the latter achieving locoregional control. Results of induction chemotherapy followed by CRT are encouraging, and suggest a reasonable toxicity profile, lower distal failure rates and improved survival in comparison with historical controls using the same CRT regimen [22,34,35].

In a meta-analysis, induction with platinum/5-FU resulted in a small survival advantage over locoregional therapy alone. The introduction of a taxane into induction chemotherapy regimens has produced promising results. Randomized clinical trials in which the control arm is concurrent CRT and the experimental arm is induction chemotherapy followed by concurrent CRT are planned [36].

Induction chemotherapy cannot be considered standard of care due to the lack of convincing phase III evidence, but lower-level evidence suggests that it is reasonably safe and may benefit patients at high risk for distal failure as indicated by advanced nodal involvement. The triplet combination of a taxane, cisplatin and 5-FU seems to have a high degree of activity and acceptable toxicity [37,38]. As adequate phase III evidence is not available currently, induction chemotherapy should not be used routinely in HNSCC outside a clinical trial.

Targeting the epidermal growth factor receptor (EGFR)

A complementary approach to the above treatments might be the addition of drugs that may further improve their efficacy. The EGFR is a member of the erbB family of receptor transmembrane glycoproteins that play an important role in cell growth and differentiation using tyrosine kinase activity as the signal transduction mechanism. Phosphorylated EGFR and its substrates activate signal transduction pathways leading to the proliferation, survival and motility of cells, and their progression to invasive disease and metastasis [39–41].

Overexpression of the EGFR has been shown to be a characteristic feature of HNSCC, and this in turn has been correlated with a poor prognosis and resistance to radiotherapy [42,43]. High levels of expression of the EGFR are associated with a poor prognosis and poor response to radiotherapy. Indeed, the important role of EGFR in mitogenesis, angiogenesis, migration and invasive capacity of human malignancies make it an ideal target for therapy using anti-EGFR monoclonal

antibodies (mAbs) or small molecule tyrosine kinase inhibitors [44]. EGFR inhibitors hold promise in two important ways: (a) to further improve efficacy for patients at risk for recurrence and (b) to decrease treatment-related toxicities by replacing more toxic drugs without jeopardizing survival [45]. There are currently several molecular therapeutic strategies against EGFR, some of which are at an advanced stage of clinical development. A number of these strategies are discussed below.

EGFR-specific mAbs

Cetuximab

In the early 1980s, a number of mouse mAbs were developed against the external domain of the EGFR [46]. Among them, cetuximab was very effective in inhibiting the binding of ligands to the EGFR, thereby blocking the ligand-induced tyrosine phosphorylation of the receptor, and inhibiting the growth *in vitro* and *in vivo* of a panel of EGFR-overexpressing tumor cell lines [47].

Cetuximab adds to the activity of radiotherapy in locoregional head and neck cancer, and when given with platinum-based chemotherapy is active in a proportion of patients with platinum-refractory recurrent or metastatic HNSCC, as is cetuximab monotherapy [48].

The results of three phase I clinical trials with cetuximab as a single dose, multiple weekly dose and multiple dose in combination with cisplatin in 52 patients, including 26 with head and neck cancers, demonstrated that the saturated dose had minimal toxicity which was not related to the dose level or the number of cycles administered [47]. The result of two phase II studies in patients with advanced head and neck cancer, who were progressing following chemotherapy, showed a response rate of 11 (75) and 23% ($n = 75$), respectively [43]. In a study involving 500 patients, cetuximab caused tumors to regress 11% and delayed tumor growth by 1.5 months.

In a recent study by Herbst *et al.* [49], 76 patients with stable or progressive disease on cisplatin/paclitaxel or cisplatin/fluorouracil treatment went on to receive combination therapy with cetuximab (400 mg/m^2 i.v. on day 1, then 250 mg/m^2/week) and cisplatin (75 or 100 mg/m^2 i.v. on day 1 and q3 weeks). Twenty percent of patients with progressive disease and 18% of those with stable disease achieved an objective response, with mean overall survival times of 6.1 and 11.7 months, respectively. Cetuximab/cisplatin was shown to be an active regimen in refractory SCCHN.

Baselga *et al.* [50] also looked at the efficacy and safety of cetuximab in combination with platinum-based chemotherapy in patients with platinum-refractory recurrent or metastatic SCCHN. Ninety-six eligible patients received cetuximab (initial dose of 400 mg/m^2 followed by subsequent weekly doses of 250 mg/m^2) followed by platinum chemotherapy at the same dose and schedule at which progressive disease was documented before entry into the study. The response rate was 10%, with a disease-control rate of 53%. The median time to progression and overall survival were 85 and 183 days, respectively.

A phase II study by Trigo *et al.* [51] in 2004 demonstrated that cetuximab monotherapy induces an even better response rate (16.5%) and a similar disease control rate (53.4%) with respect to combination studies in a similar patient population.

Acneiform skin rash is the most common toxicity which is found with several of the EGFR inhibitors [43]. Several phase III clinical trials with cetuximab in patients with advanced head and neck cancer are currently underway [53].

A phase III multicenter trial [54] enrolled 424 patients with stage III/IV HNSCC, randomizing them to receive radiotherapy with or without concomitant cetuximab as a primary treatment. Overall, the regimen was well tolerated, with an increase in grade 3 cutaneous toxicity from 18 to 34% and some mild increases in allergic reactions. Even though only preliminary data are available, a marked increase in overall survival from 28 months with radiation alone to 54 months with the addition of cetuximab was reported. Locoregional control was significantly improved in the cetuximab arm as well (48 compared with 56% at 2 years, $P = 0.02$). These reports are very encouraging; however, the major difficulty in interpreting this data is that it remains unclear how radiotherapy plus cetuximab compares to CRT. Given the immature nature of the data, it is prudent to wait until further information becomes available. A large phase III trial of cetuximab combined with irradiation in locally advanced head and neck cancer has completed recruitment. Data for this trial are awaited [55].

Matuzumab

In the mid-1980s, the mouse IgG2a anti-EGFR was developed. This antibody is directed against the external domain of EGFR in human SCCA [56]. The results of preclinical trials with this antibody demonstrated that it blocks the binding of the ligands to the receptor, inhibits the ligand-induced tyrosine phosphorylation of the receptor and inhibits the growth of human EGFR cell lines of HNSCC origin, with additive effect with cisplatin [57,58]. On the basis of encouraging preclinical trials, a phase I clinical trial with a single dose of this antibody was conducted in 12 patients with advanced laryngeal or hypopharyngeal carcinoma. All patients tolerated the single-dose administration of this antibody very well. In addition, good homogeneous binding of this antibody to

the primary lesions and lymph node metastasis was demonstrated 3 days post-treatment [59].

In a phase I study by Vanhoefer *et al.* [60], 22 patients were treated with matuzumab at five different dose levels. Objective response (23%) and disease stabilization (27%) were achieved at all dose levels, and responding patients received treatment for up to 18 months without cumulative toxicity.

Panitumumab (ABX-EGF)

Panitumumab is the first high-affinity fully human mAb that has been developed against human EGFR by Abgenix California, USA using Xenomouse mice [61]. This mAb has been shown to block the binding of ligands to the EGFR, to inhibit tyrosine phosphorylation of the EGFR, and to inhibit in-vitro and in-vivo growth of EGFR-expressing tumors. Several clinical trials are currently underway with this antibody in patients whose tumors express EGFR in more than 10% of tumor cells. The predominant toxicity has been transient acneiform skin rashes, which are also considered as a marker of clinically relevant EGFR targeting and its saturation *in vivo* with other EGFR inhibitors.

Small-molecule tyrosine kinase inhibitors (TKIs)

TKIs are another generation of antigen-specific drugs with great potential for the treatment of HNSCC. Unlike the anti-EGFR mAbs that inhibit growth by blocking the binding of growth factors to the extracellular domain of the receptor, small-molecule TKIs are directed against the intracellular domain of the receptor. By binding to such domains, TKIs may inhibit the tyrosine phosphorylation of such receptors by a reversible or irreversible mechanism. As a result, it is envisaged that further therapeutic benefit may be obtained by simultaneous targeting of both the extracellular and intracellular domains of the receptor with a combination of small-molecule TKIs and mAbs [62].

Gefitinib

Gefitinib is the first orally active, selective epidermal growth factor inhibitor that has been approved in Japan (2002) and then in the US by the FDA (2003) for the treatment of advanced non-small cell lung cancer [63]. In preclinical studies, gefitinib has been shown to (i) inhibit the growth *in vitro* and *in vivo* of a panel of cell lines expressing high, intermediate or low levels of the EGFR, and (ii) to have additive or synergistic properties in combination with cytotoxic drugs and radiotherapy [64,65].

Preclinical studies have also evaluated the anti-tumor activity of gefitinib combined with cytotoxic agents [66]. When gefitinib was applied either before or concurrently with 5-FU and/or cisplatin in two head and neck cell lines, the effects on cell growth were at least additive, with the best results achieved when gefitinib was applied both before and during exposure to both cytotoxic agents [67].

In contrast to the results of the preclinical trials however, the results of two large phase III trials, with more than 2000 patients, with gefitinib in combination with advanced NSCLC were disappointing. The combination offered no additional benefit over the use of chemotherapy alone [68,69]. The result of this clinical trial highlighted the need for further studies on the selection of a specific population of responsive patients, identification of predictive factors and a better preclinical model for treatment with TKIs [70].

The discovery that patients with exon 19 and 21 mutations in the EGFR gene have around an 80% response rate to gefitinib, and that this response confers survival benefit, indicates its potential utility for mutation-positive patients with advanced- and earlier-stage disease [71]. Clinical characteristics, such as never smoking status and histology, can also identify individuals likely to respond to EGFR TKIs [72].

A phase II study evaluating gefitinib as first- or second-line monotherapy in patients with advanced head and neck cancer has been completed [73]. Approximately 50% of the 47 evaluable patients had failed prior chemotherapy (typically platinum based) for recurrent/metastatic disease. The results with gefitinib are more favorable than those achieved with chemotherapy in this setting, with the additional benefit of greatly reduced treatment-related toxicity [55]. A phase II study of 250 mg gefitinib in advanced HNSCC [74] demonstrated that this dose is well tolerated, with modest benefit and without significant deterioration in overall quality of life scores.

Another trial exploring the combination of gefitinib and radiation with or without cisplatin is currently ongoing, and demonstrates that the combination of gefitinib with cisplatin and radiotherapy appears feasible [75].

Erlotinib

Erlotinib is an orally available, reversible inhibitor of the EGFR tyrosine kinase domain and is at an advanced stage (phase III) of clinical development in a wide range of cancer patients including those with HNSCC [53,76]. Erlotinib inhibits the growth *in vitro* and *in vivo* of a panel of EGFR-overexpressing cell lines, and has been shown to induce synergistic effects in combination with cytotoxic drugs. In preclinical studies, the anti-tumor activity of this agent has been associated with its ability to inhibit the phosphorylation of the EGFR tyrosine kinase domain [77].

In a phase II trial, efficacy and safety profiles of erlotinib were investigated in 115 patients with advanced recurrent and/or metastatic HNSCC, regardless of their EGFR status. Partial responses and disease stabilization were maintained in 4.3 and 38.3% of the cases, respectively, with 6% of patients undergoing dose escalations and 46% requiring dose reductions and/or interruptions. The most common drug-related toxicities (rash and diarrhea) were detected in 79 and 37% of patients, respectively [45].

Treatment of tumor cells expressing high levels of EGFR with erlotinib has, as with other EGFR inhibitors, been shown to make such cells radiosensitive [78]. This in turn would suggest that this compound might also have a role in the treatment of HNSCC patients in combination with radiotherapy. Several phase II–III studies with this compound are currently underway.

Other TKIs

In addition to the reversible TKIs such as the ones described above, there are currently several other types of small-molecule TKIs in different stages of preclinical and clinical development. While some of these compounds are highly specific for the EGFR, others inhibit signal transduction through all members of the EGFR family. It remains to be seen whether small-molecule inhibitors of the EGFR family would have a better therapeutic effect than those molecules that are highly specific for one member of the EGFR family [44].

There is a strong rationale for targeting EGFR in HNSCC and this rationale has been validated in extensive preclinical studies, which have shown that EGFR inhibitors such as gefitinib and erlotinib are active as monotherapy, and that mAbs such as cetuximab are additive/synergistic in combination with radiotherapy or chemotherapy. The initial clinical results with EGFR inhibitors in head and neck cancer are promising [55]. The promising results of the early clinical studies with EGFR inhibitors in head and neck cancer need to be established in phase III studies, the results of which are eagerly awaited. It is hoped that the results of these trials, which will mature over the next few years, will help determine the optimum use of EGFR agents in head and neck cancers.

While overexpression of the EGFR is a hallmark of HNSCC, chronic treatment of the EGFR-overexpressing tumors with EGFR inhibitors, as with treatment with cytotoxic drugs, may also result in the development of a phenotype resistant to further treatment with such inhibitors. It is therefore important to identify a panel of markers of biological and clinical significance that can be used not only in the selection of patients who would gain benefit from EGFR inhibitor therapy, but also those patients whose tumors may become resistant to the treatments.

Angiogenesis inhibitors

Compounds with anti-angiogenic properties of different origin and with different mechanisms of action have been identified and validated in preclinical models. Strategies to inhibit vascular endothelial growth factor (VEGF) activity include toxin conjugates to VEGF, soluble VEGF receptor, peptides that interfere with VEGF binding, anti-VEGF mAb (bevacizumab) and small TKIs that block intracellular VEGF receptor signaling. Bevacizumab is a recombinant humanized mAb which has been shown to be safe when administered in combination with chemotherapy [79]. The clinical efficacy of bevacizumab in colon cancer in combination with chemotherapy caused a revival of the anti-angiogenic strategy. By combining this agent with a tyrosine kinase receptor EGFR blocker (erlotinib), remarkable responses were seen in renal cell cancer. [80] Similar trials are now underway in head and neck cancer.

Cyclooxygenase (COX)-2: another bull's eye?

Another group of drugs with anti-neoplastic activities are non-steroidal anti-inflammatory drugs (NSAIDs). One property shared by all such drugs is their ability to inhibit COX, a key enzyme required for the production of prostaglandin (PG) from arachidonic acid [81]. PGs have been shown to play an important role in the pathogenesis of cancer by stimulating cell proliferation and motility, inhibiting apoptosis and immune surveillance, and inducing angiogenesis. Of two COX isoforms, COX-1 is expressed constitutively in a number of normal cell types and tissues. In contrast, COX-*2* is undetectable in most normal tissues, but is rapidly inducible in response to various mitogenic and inflammatory stimuli (e.g. cytokines, oncogenes, hypoxia, carcinogens) [81]. High levels of COX-*2* have been associated with lymph node metastasis, a poor prognosis and a poor response to radiotherapy in patients with HNSCC [82]. Recent data also demonstrates that COX-*2* is selectively upregulated in DNA aneuploid oral dysplastic lesions and in oral cancers, but not in normal oral tissue [83]. These findings suggest that COX-*2* is upregulated during malignant transition of mucosa and in a manner related to genomic instability.

Indeed, as the expression of COX-*2* has been shown to correlate with the expression of EGFR levels, angiogenesis and metastasis in patients with head and neck cancer, such data provide further support for the use of therapeutic strategies that involve the use of EGFR inhibitors in combination with a COX-*2* inhibitor and the inhibitor of angiogenesis in patients with HNSCC [84,85]. Such combination strategies may not only improve the poor response rate in cancer patients, but also could prevent the development of a resistant phenotype that is often associated with the use of a single drug [44].

The combination of EGFR-selective TKIs (Iressa or gefitinib) with a COX-2 inhibitor (Celebrex) either additively or synergistically inhibited the growth of HNSCC cell lines, significantly induced apoptosis and suppressed capillary formation of endothelium [86]. Non-selective COX-inhibiting NSAIDs remain very promising cancer prevention agents since they inhibit COX-2 and do not appear to increase cardiovascular disease risk [87].

In summary, the following rationale supports combined EGFR and COX-2 inhibition to prevent head and neck cancer; preclinical models of human head and neck cancer have demonstrated the antitumor effects of EGFR and COX-2 targeting. Additionally, a phase I study of gefitinib plus celecoxib in recurrent or metastatic HNSCC demonstrated that *22%* (four out of 18 patients assessable) achieved a confirmed partial response [88].

Molecular therapy of HNSCC

Novel therapeutic approaches based on our increasing understanding of the molecular changes that underlie the development of cancer have the potential to improve prognosis.

Cancer gene therapy (CGT) involves the delivery of genetic sequences into tumor cells for a therapeutic purpose. A number of viral and non-viral vectors have been developed that have the ability to deliver therapeutic genes specifically to tumors. These therapeutic genes can exert their effects by correcting existing genetic abnormalities, by killing cells directly or indirectly through recruitment of the immune system.

HNSCC is an ideal model system in which to develop CGT strategies. HNSCC is usually a locoregional disease at presentation in which the tumor is restricted to the primary site and/or the regional cervical lymph nodes. Even at relapse, the disease generally remains in the head and neck region, and presents with disease at or close to the body surface. It is therefore amenable to intratumoral injection of gene delivery vectors and/or tissue biopsy to monitor gene expression and therapeutic efficacy.

Gene therapy for head and neck cancer

Viruses have evolved to infect cells, and to commandeer their biosynthetic pathways for viral replication, packaging and release. Many viral vectors are being studies, including replication-defective viral vectors and genetically engineered replication-competent viral vectors. A replication-competent virus with inherent tumor specificity has undergone assessment in a phase I trial using i.v. administration in patients with advanced solid cancers, including HNSCC [89]. Toxicity was largely limited to a flu-like illness and transient hypotension. There were two responses, including a complete response in a patient with SCCA of the tonsil. Several non-viral vectors are also under study. Strategies that have been used include the use of naked plasmid cDNA either alone or coated on to gold particles, or liposomes that contain cationic lipids. Unfortunately, they suffer from low transduction efficiency and mediate only transient gene expression [90].

Mutations of tumor-suppressor genes (TSGs) are very common in cancer. These genes are critical regulators of normal cell biology and are important determinants of cellular responses to treatment.

The archetypal TSG is p53, the nuclear phosphoprotein that protects the cell against genotoxic stress by inducing a G_1/S cell cycle arrest that allows time for DNA repair mechanisms to correct any damage that has been sustained [91]. Delivery of wild-type p53 can sensitize cancer cells to radiotherapy [92] and chemotherapy [93] both *in vitro* and *in vivo*. p53 replacement therapy with an adenovirus containing wild-type p53 has shown promise in a phase I trial in advanced head and neck cancer [94]. A number of preliminary phase II clinical trials of p53 gene therapy have been performed [95]. Cayman *et al.* [95] treated 18 patients with relapsed HNSCC with intratumoral injections of a viral vector expressing wild-type p53. There was a single pathological complete response, two clinical partial responses, six patients with disease stabilization and six patients with progressive disease. The treatment was well tolerated and was largely confined to pain at the injection site. Given these encouraging early results, it is likely that clinical applications of p53 gene therapy with radiotherapy and/or chemotherapy will follow.

In addition to the work on p53, additional studies have revolved around other cell cycle control genes. Preclinical in-vitro and in-vivo studies in a number of model systems including HNSCC have demonstrated that restoration of expression of the retinoblastoma (Rb) and cyclin-dependent kinase inhibitors by a variety of vectors mediated G_1/S cell cycle arrest, apoptosis and reduced tumor growth [96].

Aberrant expression of oncogenes can confer on cells a growth advantage or the ability to circumvent normal apoptotic pathways. CGT strategies can be formulated to negate the activating function of these mutated genes by targeting the transcriptional/translational machinery of the cell with the aim of preventing the cell from making functional oncogenic proteins. Two main strategies have been proposed: (a) antisense oligonucleotides (AOs) that can interfere with either transcription or translation and (b) catalytic ribozymes that interfere with translation [90].

AOs against several oncogene families reduced the growth of tumors *in vitro* and *in vivo* alone and in combination with cytotoxic drugs [97]. As a result, AOs

have entered phase I clinical trials to define their toxicity profile [98]. Further studies of AOs need to answer questions such as what are the most promising mRNA targets, the most efficacious route(s) of administration and the role of AOs in combination with other treatment modalities.

Ribozymes are RNA molecules with catalytic activity that degrade phosphodiester bonds in mRNA molecules in a sequence specific manner. Two studies have shown activity *in vitro* in head and neck cancer lines [99,100]. As yet, there have been no clinical trials with this modality.

The immune response is particularly attractive as a target for CGT. A small immunogenic stimulus triggers a massively amplified response and the generation of memory cells could prevent disease recurrence. Clinical studies to date of immunomodulatory CGT have largely involved either delivering genes encoding cytokines directly into tumor cells *in vivo*, or using genetically modified normal or malignant cells as cancer vaccines. As an example of the former approach, intratumoral injections of cDNA encapsulated in liposomes were well tolerated in phase I and II studies, and resulted in successful gene transfer. Stable disease and some partial responses were reported in patients with HNSCC [101].

Significant advances in understanding the molecular biology of cancer have opened up a new field of study in which potential therapeutic gains may accrue from the introduction of genetic sequences into tumors or normal tissues. This approach has yielded dramatic therapeutic responses *in vitro* and in some animal models, but as yet has not had a major impact on cancer treatment. The generation of improved delivery systems and refinement of the mechanisms of controlling gene expression from them will be a key step in the clinical development of gene therapy. Integration of these new approaches into current therapeutic regimens using surgery, radiotherapy and chemotherapy is likely to yield the most immediate evidence of therapeutic efficacy. HNSCC is an ideal model in which to test gene therapy approaches by virtue of its tendency to present and recur locally in a form that is relatively refractory to conventional treatments, and to be amenable to direct local injection and biopsy.

Conclusion

Multimodality approaches remain the forefront of intervention for patients with advanced HNSCC. This review of selected advances in the multidisciplinary care of head and neck cancer should provide both a guideline for current approaches to patient care as well as a baseline on which future research can be built.

CRT has established itself as a central treatment modality either upfront as definitive therapy or as an adjuvant to surgery, due to its excellent local control rates, increased survival and higher rates of organ preservation. The development of customized surgical and reconstruction techniques combined with state-of-the-art radiation techniques such as three-dimensional conformal radiation therapy and intensity-modulated radiotherapy logically are bound to boost the benefit accrued by high-risk patients from adjuvant concurrent CRT. The integration of EGFR inhibitors is poised to play an increasingly important curative role, while potentially decreasing toxicity. The challenge is the identification of reliable EGFR response predictors and in the identification of the 20–30% of the patient subpopulation whose tumors are EGFR dependent, and would, therefore, benefit from therapy with the EGFR inhibitors in combination with other forms of therapy.

Future regimens will certainly include therapies directed at the roots of molecular carcinogenesis such as growth factors, cell death machinery and angiogenesis factors. Addition of these therapies to current regimens is already used in breast cancer and lymphoma, and is under preliminary study for head and neck cancer. The advent of non-cytotoxic drugs, the delivery of more efficacious cytotoxic agents, the optimization of multidrug regimens and the application of modern techniques of radiation therapy are the tools we have now to test in our quest to control disease locally and eradicate occult micrometastases.

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