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REVIEW ARTICLE

Biomarkers predicting chemotherapy response in head and neck squamous cell carcinoma: a review

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Abstract

Background: Biomarkers are increasingly being used in many cancers to select patients for oncological treatment paradigms based on their inherent genetic properties. However, in head and neck cancers, there are no personalised therapies available outside the context of a clinical trial. A number of studies suggest there are intrinsic tumour properties of head and neck cancers that affect their response to chemotherapeutic agents. This paper aimed to review their evidence base.

Method: A narrative review was conducted following a search of the PubMed database.

Results and conclusion: The review identified a number of biomarkers predicting response to chemotherapy in head and neck cancers. The paper discusses these in detail, and explores where future research could be directed in order to deliver personalised therapies for patients with head and neck cancers.

Key words: Otorhinolaryngological Neoplasms; Induction Chemotherapy; Biological Markers

Introduction

Biomarkers are measureable characteristics that provide objective indications of disease states or severity. Their use is already evident in cancer therapeutics, from the pioneering discovery of the human epidermal growth factor receptor 2 monoclonal antibody trastuzumab, which is effective in human epidermal growth factor receptor 2 positive breast cancer,[1] to the use of epidermal growth factor receptor inhibitors in metastatic colorectal cancers[2] and, more recently, BRAF inhibitors in BRAF V600E mutated melanomas.[3] These findings take us a step closer to truly personalised medicine.

In the head and neck, a number of potential prognostic biomarkers[4] are being prospectively studied within clinical trials.[5] However, the only established head and neck biomarkers are surrogates for the human papilloma virus (HPV), such as p16; patients with HPV-positive head and neck disease have a survival advantage following either surgical or non-surgical treatments.[6,7] Nevertheless, HPV positivity does not at present influence management outside of a clinical trial setting.

Numerous studies are beginning to address the role of biomarkers in predicting responses to chemotherapy, radiotherapy and chemoradiation therapies in head and neck squamous cell carcinoma (SCC). Given that there is at least some consensus from the head and neck cancer community that platinum-based chemotherapy may not be a necessity in the treatment of head and neck disease,[8] we aimed to review the role of biomarkers in predicting chemotherapy response in head and neck SCC in order to better stratify our patients to treatment regimens.

Materials and methods

To produce this narrative review, the search terms in Table I were inputted into the PubMed database. Additional bibliographic referencing was undertaken.

Induction or neoadjuvant therapies

Head and neck SCC chemotherapy is almost always confounded by concurrent radiotherapy. This review is therefore focussed on the smaller volume of trial literature concerning the role of induction (pre-chemoradiotherapy) and neoadjuvant (pre-surgery) chemotherapy on responses to treatment in head and neck SCC.

p53 and Bcl-xL expression

The tumour suppressor protein p53 is one of the most commonly studied biomarkers in the head and neck. Following promising clinical case series data,[9,10] Perrone and colleagues reviewed TP53 gene mutations in patients enrolled in a randomised, controlled trial of neoadjuvant and induction chemotherapy in oral cancer.[11] They analysed TP53 status in complete

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TABLE I
SEARCH TERMS INPUTTED INTO PUBMED DATABASE

Population terms
Head and neck neoplasms
Otorhinolaryngologic neoplasms
Oral cavity neoplasms
Oropharynx neoplasms
Hypopharynx neoplasms
Larynx neoplasms
Intervention terms
Chemotherapy
Induction chemotherapy
Neo-adjuvant chemotherapy
Cisplatin
Fluorouracil
Carboplatin
Cetuximab
Erbitux
Comparator terms
Biomarkers
Cytodiagnosis
Immunohistochemistry
Neoplasm proteins
Molecular biology
Molecular sequence data
Viral gene
Viral gene, tumor suppressing
DNA methylation
Oncoprotein p53
Tumor suppressing gene
Tumor suppressing proteins
Promotor regions
DNA mutational analysis
Genomics
Outcome terms
Local-regional control
Survival analysis

surgical resection specimens of 'stable' or 'progressing' tumours. The authors compared those with and without pathological complete regression (the latter was defined as no evidence of tumour on the surgical resection specimen). They found that a higher rate of pathological complete regression was associated with the presence of wild type TP53. However, it would appear that patients with functioning p53 also do better when treated with primary surgery, suggesting that this benefit is not chemotherapy-specific. Furthermore, the treatment protocol was criticised for the inadequate assessment of TP53 gene mutations at exon 4, known to be associated with chemotherapeutic response.[12]

More recently, findings from multivariate analyses of a number of apoptotic markers, including p53, suggested that these biomarkers have little prognostic value,[13] and that p53 may not be an appropriate biomarker for treatment stratification. However, data from a randomised, controlled trial[14] and a case series[15] following induction chemotherapy in laryngeal and oropharyngeal cancers seem to indicate that whilst p53 mutations are not prognostic in themselves, a combination of low expression of p53 and high Bcl-xL seems to follow a 'high risk' pattern, with decreased overall and disease-specific survival. Unfortunately, neither study commented on the role of these combined markers on pathological tumour response to induction or neoadjuvant chemotherapy.

Epidermal growth factor receptor expression

Kumar and colleagues conducted a prospective analysis of trial data investigating induction chemotherapy, to select patients with a good response for chemoradiotherapy. They found that low epidermal growth factor receptor expression was associated with a greater pathological response (over 50 per cent tumour volume reduction at the primary site on imaging) following platinum-based induction chemotherapy in 66 patients treated for oropharyngeal cancer.[15] This was independent of age, sex, tumour stage, nodal stage and smoking status.

Epidermal growth factor receptor has been further studied retrospectively in the context of induction and neoadjuvant chemotherapy by: Etienne *et al*., in 61 patients;[16] Hitt *et al*., in 46 patients;[17] and Pivot *et al*., in 71 patients.[18] All three studies showed that low levels of epidermal growth factor receptor independently correlated with survival, although interestingly not for the proportion of patients with complete or partial pathological response.

Given these findings, it is tempting to propose that epidermal growth factor receptor expression has at least a prognostic and potentially predictive role to play in chemotherapy response in head and neck SCC. Logic would suggest that if low levels of epidermal growth factor receptor correlate with good outcomes, it would be worth investigating whether direct inhibition of epidermal growth factor receptor pathways could improve survival in this patient group. Unfortunately, randomised, controlled trial data of 312 patients gathered by Licitra and colleagues failed to reveal a survival association between epidermal growth factor receptor copy number and response to combined cisplatin and the epidermal growth factor receptor inhibitor cetuximab.[19]

It has therefore been postulated that concomitant inhibition of epidermal growth factor receptor independent survival pathways may be needed to achieve a beneficial clinical effect.[20] This is well recognised in other diseases such as colorectal cancers, where patients with mutated k-ras pathways do not respond favourably to cetuximab.[2] Until the biology of epidermal growth factor receptor dependent and independent pathways are further understood in the context of co-inhibition, there is no biomarker that can predict response to epidermal growth factor receptor inhibitors in head and neck SCC.

Cyclin D1

Cyclin D1 is an important regulator of cell proliferation that promotes advancement through the G_1 phase of the cell cycle and has been shown to be implicated in resistance to cisplatin.[21] In a retrospective study of 224 patients undergoing either induction or neoadjuvant cisplatin chemotherapy followed by radiotherapy, or

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surgery followed only by radiotherapy, low expression of the CCND1 gene coding for cyclin D1 was an independent predictor of chemotherapy response (both complete and partial (over 30 per cent tumour reduction) response) and survival in the induction or neoadjuvant group.[22] CCND1 further helped predict response to surgery; patients with high CCND1 expression had a relative survival benefit in the surgical group, more so than in the neoadjuvant group.

This provides some evidence that head and neck cancers expressing low levels of CCND1 may benefit from neoadjuvant chemotherapy, whilst those with high expression may benefit from primary surgery. It is worth appreciating though that patients' HPV status, an important covariate, was unknown. Nevertheless, oropharyngeal disease, which has the highest HPV positivity, was roughly equal in both treatment groups. There is also a possibility of under-treatment in both groups. No patients in the surgery group received chemotherapy, and there was no suggestion as to which patients may have had indications for post-operative chemotherapy. In addition, patients in the neoadjuvant arm only received two doses of chemotherapy followed by radiotherapy (rather than concurrent chemoradiotherapy). Nevertheless, the role of cyclin D1 has been replicated in other similar, but smaller studies.[23,24]

Despite these promising results, it is noteworthy that multivariate analysis involving a number of markers, including cyclin D1, has suggested that there is no prognostic or predictive benefit for cyclin D1 expression status in oral or oropharyngeal SCC.[13]

Beta tubulins

Beta tubulins are essential components of the cell cytoskeleton that also play a crucial role in mitosis; they form the mitotic spindle that allows chromosomes to separate during cell division.[25] Various anti-cancer drugs have been developed to bind to the tubulins to prevent mitosis, and levels of beta tubulins correlate well with response to chemotherapy.[26]

A retrospective review of biomarkers was performed in 265 patients recruited to the Tax 324 study, which was designed to compare 2 different induction and neoadjuvant chemotherapy regimens.[27] Survival was the principal outcome, and low beta tubulin II expression seemed to correlate with significantly enhanced progression-free survival. This effect was independent of, and greater than, other potential tumour markers such as p53 and Bcl2. The effect size was greatest in those treated with a triple induction chemotherapy regime (cisplatin, 5-fluorouracil and docetaxel *vs* cisplatin and fluorouracil), raising the question of whether beta tubulin II expression can predict sensitivity to platinum-based chemotherapy and identify patients who may benefit from taxane-based chemotherapy.

Other classes of beta tubulins have also been implicated in chemotherapy-related survival in head and neck SCC,[28] lung cancers,[29] and ovarian cancers.[30] However, most of the data focus on the impact of beta tubulins on the response to taxanes and vinca alkaloids, given that their anti-tubulin effects are their main mode of action.[26] As cisplatin also exerts an anti-tubulin effect, this warrants further study.[31] In addition, data on the role of beta tubulins in predicting response as opposed to survival are needed if beta II tubulins are to be used to stratify patients to receive chemotherapy in the induction or neoadjuvant setting.

Other genetic polymorphisms

Ziliak and colleagues attempted full genome sequencing in the head and neck to look for polymorphisms that may be associated with response to induction or neoadjuvant chemotherapy.[32] They studied 179 International HapMap lymphoblastoid cell lines, which have undergone complete genetic sequencing, to investigate sensitivity *in vitro* to carboplatin. Two single nucleotide polymorphisms associated with carboplatin sensitivity were identified and validated against a clinical response in 52 patients enrolled in a trial of induction chemotherapy for head and neck cancers. The two single nucleotide polymorphisms – rs6870861 and rs2551038 – were associated with a number of genes, including those known to be implicated in platinum uptake and clearance. However, the study impact was limited as it did not clearly define what was meant by 'response' to chemotherapy.

This study design has further been utilised to investigate other cancers, with different single nucleotide polymorphisms identified.[33] This, coupled with the very large single nucleotide polymorphism number in a genome, raises the important possibility of type I errors. Whilst full genome sequencing provides an interesting study design by which to identify possible targets for treatment stratification or pharmacological selection, validation with large clinical cohorts accounting for known prognostic or predictive markers is required.

Angiogenesis

Tumour angiogenesis has also been shown to be a predictive marker of response to induction chemotherapy. A retrospective analysis of a limited number of pre-treatment biopsies from the Veteran Affairs laryngeal trial showed that a lower density of microvessels correlated with an improved partial (over 50 per cent volume reduction on imaging) and complete response to induction chemotherapy.[34] This might initially be considered a paradox given that increased vasculature may have been thought to promote drug delivery. However, one plausible explanation for these alternative findings is that the decreased availability of nourishing vessels available in the tumour microenvironment may be inhibiting growth.[34]

Vascular endothelial growth factor, another biomarker associated with neoangiogenesis, has also been studied in the context of induction chemotherapy.

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Forty-nine patients with advanced laryngeal cancer were treated by induction chemotherapy using the same protocol as in the Veteran Affairs trial.[35] Response to therapy was correlated with low immunohistochemical levels of vascular endothelial growth factor. However, it appears that these effects are not only limited to chemotherapy; low vascular endothelial growth factor levels have also been shown to correlate with improved overall survival in patients with with head and neck cancer with or without chemotherapy.[36,37]

Glutathione enzyme expression

The glutathione pathway has been associated with sensitivity to platinum-based chemotherapeutic agents in the head and neck. A number of translational study designs have demonstrated that glutathione is inversely correlated with cisplatin sensitivity. This raises the possibility that low levels of glutathione might predict response to induction chemotherapy. The mechanism of this resistance could be related to glutathione conjugation with platinum compounds, which thus reduce the DNA damaging effects of cisplatin or enhance the ability to recover from the DNA damaging effects of chemotherapeutic agents.

An early study by Nishimura and colleagues investigated the expression of glutathione S-transferase in 51 pre-treatment biopsies of patients who underwent chemotherapy.[38] The study found greater response (both complete and partial (over 50 per cent reduction in tumour volume) response) to chemotherapy in those with low glutathione S-transferase expression. Indeed, in the 23 patients for whom the chemotherapy was given in the neoadjuvant setting, all 14 patients with low glutathione S-transferase expression had responded to cisplatin, compared with only 4 of 9 patients with high glutathione S-transferase expression.[38] Low glutathione S-transferase expression was also a response predictor in patients given neoadjuvant chemotherapy for head and neck recurrence.

These findings are supported by other studies, although, interestingly, resistance was better predicted by p53 mutation in more advanced disease than by glutathione S-transferase expression.[39] However, conflicting results have also been reported; a further analysis of 68 patients undergoing induction chemotherapy found that low levels of glutathione S-transferase messenger RNA by in situ hybridisation correlated with survival, but not pathological response to chemotherapy.[40]

Metallomatrix proteases

Metallomatrix protease mutations have also been associated with an improved response to chemotherapy in the neoadjuvant setting.[41] In a study of 148 tumours at a number of different sites, it was found that mutations of metallomatrix protease 3 were associated with improved response (over 50 per cent reduction in tumour volume on imaging) to induction chemotherapy, independent of other mutations such as p53 and tumour stage, possibly through apoptosis triggered by the Fas/Fas ligand pathway. However, this study consisted of a large number of oropharyngeal cancers, and although there was no significant difference between tumour sites and response to chemotherapy, there was a trend for oropharyngeal cancers to have fewer non-responders than other sites, raising the possibility of HPV positivity as a confounding, uncontrolled variable.

Future role of biomarkers

Although a number of these studies have demonstrated that biomarkers can be used to predict chemotherapy response or aid prognosis in the induction chemotherapy setting, none of these biomarkers are ready to be used in the selection of patients for treatment paradigms. One of the main reasons for this is the large variation in responses to therapy, despite statistically significant predictive or prognostic values. For example, in a study of p53 status by Perrone and colleagues, the presence of functional p53 was significantly associated with higher levels of complete response to cisplatin therapy.[11] However, from the primary data source, we calculated sensitivity, specificity, and positive and negative predictive values for wild type p53 when predicting a pathologically complete response in oral SCC cases as 73 per cent, 52 per cent, 38 per cent and 83 per cent respectively. If the study had selected patients based on their p53 status, 29 of the 53 patients would have been selected for chemotherapy, with 18 (62 per cent) of those experiencing all the side effects of treatment with no therapeutic benefit. Furthermore, four patients would not have received chemotherapy, despite the possibility of complete response. Clearly, p53 does not work in this context to stratify patients to treatment, but there is currently no standard of predictive accuracy that would be required to begin stratifying patients to different treatment groups.

One further problem with these biomarker studies is defining what constitutes a pathological response. Whilst the consensus in many of the clinical studies seems to include a percentage of pathological regression (30–50 per cent) on imaging, there is no standardisation of reporting. Should a further large-scale induction chemotherapy trial go ahead, there needs to be a way of knowing how to assess disease response (and how large that disease response needs to be) before assigning patients to treatment groups (i.e. further doses of chemotherapy, radiation and/or surgery). There are currently reporting guidelines for detailing responses in oncology for this.[42] However, there is little evidence as to the clinical importance of specified amounts of tumour reduction and little to determine stratification thresholds for subsequent treatment. It is also not clear as to when to image patients in the context of induction chemotherapy to detect these changes. We need further

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information on how to address these points before future studies can be considered valid and large-scale randomised, controlled trials can be appropriately constructed.

Survival versus survivorship

One of the key drivers for the adoption of induction chemotherapy has been the perceived benefit of organ preservation (i.e. retaining the larynx for laryngeal cancers). However, it has become clear that dysphagia is a major side effect of non-surgical management of head and neck cancers,[43] with many patients requiring long-term feeding tubes.[44] About 30 per cent of patients undergoing 'organ-preserving' chemoradiation for laryngeal cancers also require subsequent salvage surgery.[45] This is associated with poor survival outcomes,[46] and up to two-thirds of patients experience significant complications.[47]

The dogma that chemoradiation is an organ-preserving treatment is therefore dwindling, particularly given that patients themselves rate functional outcomes as more important than whether they have chemoradiotherapy or primary surgery.[48] Indeed, in some cases, unselected patients treated with primary surgery have better swallowing outcomes than those undergoing chemoradiotherapy.[49] Selecting patients for treatment arms, to undergo therapy for which they are most likely to respond, will ultimately prevent unnecessary chemoradiation if the cancer is resistant to treatment and contribute to better surgical outcomes if operating on a patient who has not previously been irradiated.

'PREDICTR HNC' project

One non-randomised, longitudinal study currently in follow up in the UK, the 'PREDICTR HNC' project (entitled 'Improving treatment selection using predictive and prognostic classifiers of treatment response for head and neck cancers and dysplasia') aims to review a number of biomarkers (the specific biomarkers to be studied are not in the protocol) in head and neck cancer to see how patients respond to different treatment regimens.[5] Although one of its aims to develop a set of variables that may help predict responses to chemoradiotherapy or surgery, there are a large number of variables involved, including concurrent treatment with chemoradiation. Therefore, its use in identifying biomarkers to stratify patients for treatment is questionable. Nevertheless, it may reveal some important biomarkers to feed into future randomised trials that may lead to predictive treatment algorithms.

Conclusion

The role of biomarkers in the induction and neoadjuvant setting is not yet well established. A number of biomarkers have been proposed, but no markers are currently in clinical use. Future research should involve collaboration with basic science colleagues for the development of novel biomarkers for head and neck cancer. These can be evaluated against clinical outcomes retrospectively. Once these markers have been evaluated in the laboratory, randomised, controlled clinical studies should be conducted. These need to have a biomarker component and should be designed to predict which patients may respond to therapy, rather than only providing prognostic information. Finally, biomarkers should be evaluated with multivariate analyses and correlated with clinical markers known to predict disease outcomes.

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