Review

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Is there still a role for neoadjuvant chemotherapy in head and neck cancer?

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After ~20 years of conflicting results from chemotherapy in randomized trials in advanced head and neck cancer, three meta-analyses reviewed its use. All three concluded that chemotherapy was associated with a statistically significant advantage in survival, but that this was low (4% absolute benefit at 2 and 5 years). The improvement in survival was mainly based on the more robust improvement obtained with the concomitant use of chemotherapy and radiotherapy. Induction chemotherapy, in particular, was not associated with any relevant survival advantage.

This article reviews current indications for neoadjuvant chemotherapy in advanced head and neck cancer. Implications for current and future research are discussed.

Key words: head and neck cancer, neoadjuvant chemotherapy

Introduction

Head and neck squamous cell carcinoma (HNSCC) is a clinically challenging disease resulting in ~72 000 new cases and 31 000 deaths per year in the European Union in 1995, making it the eighth leading cause of cancer death and seventh for incidence [1]. Approximately 60–65% of patients with head and neck cancer can be cured with surgery and/or radiotherapy. The prognosis of an individual patient depends on the primary tumor site and extension, histotype, nodal involvement and grading [2]. In general, patients with early stage (I and II) cancer can be treated effectively with single modality treatment, while only a small fraction (30%) of patients with more advanced disease (stages III and IV) may be cured, despite extensive surgery and radiotherapy. Local regional recurrence represents the first cause of treatment failure (60%), followed by metastatic disease (up to 30%) and second primaries [3].

History of neoadjuvant chemotherapy

Over the last 25 years there has been increasing interest in treating head and neck cancer patients with chemotherapy.

One of the most surprising aspects of chemotherapy in advanced head and neck cancer is the sensitivity of squamous cell carcinoma to such therapy, in particular when administered in previously untreated patients, as in the case of the neoadjuvant setting. In the 1990s, many clinicians used neoadjuvant chemotherapy with the hope of reaching a better local control, or to improve survival, even though this was not evident from randomized studies [4]. It was only after the publications of promising data on chemoradiation and the individual patient-based meta-analysis (see below) that the general attitude towards neoadjuvant chemotherapy has changed [5].

After ~20 years of conflicting results from chemotherapy in randomized trials in advanced head and neck cancer, three meta-analyses reviewed its use. All three concluded that chemotherapy was associated with a statistically significant advantage in survival, but that this was low (4% absolute benefit at 2 and 5 years) [6–8]. The improvement in survival was mainly based on the more robust improvement obtained with the concomitant use of chemotherapy and radiotherapy (7% absolute benefit at 2 years and 8% at 5 years). Induction chemotherapy, in particular, was not associated with any relevant survival advantage either in the meta-analyses performed by Pignon et al. [8] or in that performed by El-Sayed and Nelson [7].

Based on the favorable theoretical advantages of neoadjuvant chemotherapy this failure is contraintuitive. Multiple explanations have been suggested. Looking at single studies several important flaws can be recognized. In addition to suboptimal chemotherapy regimens, available data are difficult to interpret for other reasons, such as relaxed selection criteria with respect to tumor site, tumor extension, local regional treatment, as well as low statistical power [9, 10]. In addition, during the years of clinical research, more and more sophisticated imaging tools have been introduced with major improvements in correctly staging tumors according to the TNM (tumor–node–metastasis) classification. This has been particularly the case as far as nodal extension is concerned. In this respect the so-called Will Rogers effect could have had a more favorable impact on results of more recent trials of concurrent chemoradiation than sequential approaches with neoadjuvant

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chemotherapy. Moreover, although specific computed tomographic radiological characteristics of metastatic nodes were reported to be clearly associated with different chemosensitivity and prognosis of patients treated with neoadjuvant chemotherapy, this adjunctive information was never utilized for optimizing patients selection criteria [11].

Quality of neoadjuvant chemotherapy

In Pignon's meta-analysis regarding different chemotherapy regimens, only 16 trials out of the 31 trials on neoadjuvant chemotherapy included, utilized efficient drugs such as cisplatin and 5-fluorouracil (5-FU). Pooling together the results of only these trials showed a statistically significant survival improvement of 5%, although no large single study was able to demonstrate this. Optimal induction polychemotherapy, such as with the cisplatin and infusional 5-FU (PF) regimen is able to produce a high rate of clinical response ranging from 57% to 80%, which may be associated with a high percentage (~25%) of microscopic complete response, as indicated by the microscopic examination of operative specimens. In the majority of cases these results were obtained by the administration of only three cycles of chemotherapy, which for a long time has been considered as standard in the neoadjuvant setting.

Based on these results, neoadjuvant chemotherapy was employed to investigate whether it would effectively downstage the tumor before surgery and/or radiotherapy, and by doing so would improve local control and prevent or diminish the occurrence of distant metastases. This latter effect was difficult to demonstrate, since it occurs in only a few patients and depends on the achievement of local regional control, which is the most important goal of treatment. The percentage of distant metastasis depends to a large extent on the site of origin of the primary tumor and on the type and duration of follow-up.

The specific cancer population

Two important features of this cancer population are the comorbid illnesses and the second primary tumors which occur at a constant rate of 2–3% per year. Regarding the first issue it is highly probable that only a very selected population enters prospective clinical trials and this introduces a strong bias in the interpretation of the results. Moreover, the employment of a combined treatment approach should be performed by expert oncologists, since its application in the general head and neck cancer population may be unsafe. The site of second primaries has seldom been carefully reported in studies with neoadjuvant chemotherapy and it is therefore difficult to say whether neoadjuvant chemotherapy could or could not play a role in preventing or delaying growth of subclinical second primaries. Some randomized trials employing neoadjuvant chemotherapy suggested an increased number of second primaries in the treatment arm, whereas others reported an excess number in the control arm [12–14]. Therefore, every possible role of neoadjuvant chemotherapy in that respect has to be carefully evaluated, taking into account pre-treatment examinations as well as type and duration of the follow-up as required by the study protocol. This latter aspect may not be an easy task, considering the fact that the head and neck cancer population in general is not optimally compliant with treatment and/or follow-up procedures.

Organ preservation

More favorable results were achieved when the primary end point of randomized trials was changed, i.e. reduction of functional and cosmetic deformity by treating patients with radiotherapy instead of surgery [15, 16]. It is noteworthy that a direct comparison, within a randomized trial, of surgery versus radiotherapy has never been performed in head and neck cancer.

It has been clearly shown that the integration of neoadjuvant chemotherapy contributes to organ preservation in advanced resectable disease of the larynx and hypopharynx without affecting survival. This type of approach is not widely accepted since for many clinicians the improvement of survival is to be regarded as the most important study aim [17]. This may not be the case from the patient perspective [18]. Organ preservation is obtained by treating patients responsive to neoadjuvant chemotherapy with radiotherapy alone, saving salvage surgery to cases of either failure or recurrence. It is still unknown whether these results are achieved because of an effective downstaging of the tumor, so that treatment with radiotherapy becomes more effective, or whether it acts as a selector of potentially radiocurable patients on the assumption that radiotherapy and surgery have the same probability of success, at least in selected cases. It is important to say that although a fraction of patients can be cured and preserved by radiotherapy alone, salvage surgery has to be considered as an integral part of organ/function preservation treatment strategies.

Operability and site specificity

In order to obtain biological information, medical oncologists treated patients without considering the site of origin of the primary tumor, which, on the contrary, is one of the most important aspects in the therapeutic planning for both surgeons and radiotherapists. This led to different subsites being included in one single trial. Although sharing the same histotype, it has been clearly established that particular subsites and stages have a different prognosis [19]. In one trial a survival gain was only observed in the subgroup of unresectable patients [20]. Operability is an extended concept of resectability depending on multiple factors such as TNM, anatomical tumor extension, the expected morbidity of the procedure and the surgeon's experience. Taking into consideration that an accepted definition of 'resectable tumor' is still lacking, results obtained in this ill-defined patients' category are by definition not interpretable. In this context it should be noticed that the latest 2002 AJCC cancer staging classification in fact has introduced the concept of resectability [21]. Next to the objective TNM evaluation, based on dimensions and tumor subsite involvement, the factor, resectability, is taken into account. This bears the risk of bias, particularly when it concerns so-called named 'resectable disease'. Thus, what is resectable for one surgeon may not be the case for another.

Histological tumor differentiation was demonstrated to correlate with prognosis of early stage disease treated with surgery and/or radiation. However, a different chemosensitivity could not be formally demonstrated, with the exception of nasopharyngeal cancer, in which a better response is observed and disease stages are associated with a better prognosis than comparable stage III and IV tumors arising at other sites. In more advanced disease grading or specific variables of tumor differentiation were overall not correlated with response to neoadjuvant chemotherapy, with the exception of patients achieving a complete response, in whom tumor differentiation was found to be inversely related to survival [22].

It may not be considered as fortuitous that only site-specific trials such as the organ preservation trials were able to provide a positive result, possibly indicating that head and neck cancer cannot be considered as one disease, not even from the medical oncology point of view. This statement can be corroborated by the preliminary results of the last Intergroup trial on larynx preservation [23]. In this study the arm with concomitant chemoradiation was not associated with better survival, thus calling into question the results of Pignon's meta-analysis, which indicates a significant improvement in survival through the concomitant approach in a general head and neck cancer study population.

The role of neoadjuvant chemotherapy in other specific subsites has been formally investigated in some phase II trials and in randomized trials in nasopharyngeal, oropharyngeal and oral cavity cancer [14, 24–26]. There is some evidence that it may contribute to improved survival and to avoid surgery in oropharyngeal cancer by replacing it by radiotherapy. In oral cavity cancer it may reduce the percentage of mandibulectomies and postoperative radiation as required for advanced tumors. Its downstaging effect can usefully be employed in nasopharyngeal cancer in which primary tumor volume reduction due to neoadjuvant chemotherapy may be crucial for optimal radiotherapy delivery. Nasopharyngeal cancer often spreads closely to critical structures whose tolerance dose is below what is considered as full-dose radiotherapy. Shrinkage of primary tumor, which normally occurs at the periphery of the tumor, usually allows a larger gap between tumor edge and critical structures. Therefore, even if all the pre-chemotherapy tumor volume was to be initially included in the target volume, only residual disease might be boosted to full-dose radiotherapy with potential benefit in terms of local control. This may contribute to save normal tissues from unnecessary radiation and potentially to reduce final radiation dose. This strategy has been successfully pursued by two groups [27, 28]. Moreover, recent trials in nasopharyngeal cancer would suggest an unexpected cooperative role of neoadjuvant chemotherapy in terms of improvement of local control which translates into a better survival, but not because of a reduction in distant metastases [25, 28–30].

Pathological complete response (pCR)

From the oncological point of view it seems reasonable to believe that a maximal result such as pCR has the best chance to translate into a gain in outcome. Based on the results achieved with neoadjuvant chemotherapy so far, it is likely that improvements in pCR rate will allow more successful, less aggressive, subsequent local regional therapy and might lead to its avoidance in patients with lymphomas or testicular cancer, where some patients may be cured by chemotherapy as a single modality treatment. This type of approach has been already employed by Laccourreye et al., indicating that some small selected tumors of the larynx can be cured by chemotherapy alone [31]. If these preliminary results are confirmed by other groups and by an adequate follow-up this would open a new perspective on the role of chemotherapy, at least in selected head and neck tumors. In a study conducted at the Wayne State University on 13 cases of 32 patients operated on after achieving a clinical CR with neoadjuvant chemotherapy, no residual tumor was found and all patients were free of disease at 36 months [32]. Similar outcomes were observed in two studies conducted at the Istituto Nazionale Tumori of Milan in oral cavity and paranasal sinuses tumors [14, 33]. Randomized trials have indicated that platinum-based combination chemotherapy given in the neoadjuvant setting results in a reduction of the number of cases with distant metastases. It is possible that new combinations might show better results, i.e. a higher percentage of pCRs, and have a stronger effect on micrometastases. In this respect, results of ongoing randomized trials, including taxoids + PF versus PF are awaited. However, even when these studies would end in a negative result, end points other than survival may be targeted when analyzing the role of neoadjuvant chemotherapy in this particular cancer population [34].

Molecular markers

Based on these data it is logical to look for conditions allowing to maximize the probability of obtaining a pCR. To date no clear data are available regarding the correlation between tumor subsite, grading and probability of achieving a pCR [35]. Biological predictive factors are under evaluation. First among them is the p53 status.

This oncogene is deleted or mutated in ~45% of squamous cell carcinomas of the head and neck. A germinal mutation of the p53 gene is associated with cancer predisposition, its somatic mutation pattern is used as a marker of environmental mutagens and its protein products regulate cell growth and apoptosis. Considering the fact that p53 gene alterations have been associated with environmental carcinogenesis, its relatively low rate of alterations in head and neck cancer patients is surprising, because of the invariably high exposure to environmental damages like smoke and alcohol. These data would suggest that although there may be a common origin of this type of cancer, carcinogenetic pathways may be different, thus implying different therapeutical targets and perhaps results.

p53 alteration has been shown to correlate with prognosis and with response to chemotherapy [36]. In particular, a wild-type p53 function seems to be essential for apoptosis induced by genotoxic damage such as that induced by chemotherapeutic agents and radiotherapy [37]. Some agents, such as the taxoids, are able to produce apoptosis independently from the p53 gene status, while others, such as cisplatin and radiotherapy, need a functioning p53 gene [38]. Koch et al. showed that mutations of the p53 gene are

associated with an increased risk of local regional failure after radiotherapy [39]. Similar observations have been reported in patients with colon cancer, who were treated with 5-FU, a drug which is one of the most commonly used in association with platinum components in head and neck cancer [40]. Moreover, recent observations indicate a role of p53 polymorphism in influencing cisplatin-containing chemotherapy and radiation response in advanced head and neck cancers [41]. This has important implications on future treatment with cytotoxic agents. If most employed agents in head and neck cancer need an intact apoptotic pathway, then it is easy to understand that drug resistance represents the major clinical problem. In this regard, using the p53 gene status as a therapeutic marker for indication and/or selection of drugs in the neoadjuvant setting, this will provide a new opportunity for a more tailored approach to chemotherapy. This would allow to treat with neoadjuvant chemotherapy only patients likely to gain maximal benefit from it. In the near future a global gene profiling of cancer will be possible, instead of a gene by gene approach. In this direction a cDNA microarrays analysis of 16 squamous cell tumors of the head and neck identified two major categories of cancer characterized by a great divergence in the pattern of gene expression [42]. Moreover, the specific identification of altered gene expression induced by different drugs by means of these high throughput techniques may serve as biomarkers to both predict activity of an antitumoral agent and its optimal combinations [43]. Although large-scale genotyping of tumors is still in its infancy, the use of drug-resistance markers has been already applied in some clinical settings. In the future increasing knowledge of molecular links between apoptosis and drug resistance will provide us with the basis for a new targeted cancer treatment era.

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