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Current role of chemotherapy in exclusive and integrated treatment of malignant tumours of salivary glands

Attuale ruolo della chemioterapia nei trattamenti esclusivi ed integrati dei tumori maligni delle ghiandole salivari

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Parole chiave

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Summary

In the management of salivary glands carcinomas, surgery is the treatment of choice. Post-operative radiotherapy is indicated in cases with high risk of loco-regional relapse. Radiotherapy is also standard treatment in cases that are inoperable at onset. Chemotherapy plays a palliative role. Today, the integration between radiotherapy and chemotherapy, which provides increased local control, represents a significant step forward. This integration is important since 5-year survival in tumours with high grade histology is approximately 50%. Overall incidence of metastases is approximately 25%. Primary locations of metastases are lungs, liver, bone, central nervous system and other organs. In cases of metastatic disease, chemotherapy plays only a palliative role.

Riassunto

La chirurgia rappresenta, nel trattamento dei carcinomi delle ghiandole salivari, il trattamento di scelta. La radioterapia post-operatoria è indicata nei casi ad alto rischio di recidiva loco-regionale. Inoltre la radioterapia è il trattamento standard nei casi inoperabili all'esordio. La chemioterapia ha un ruolo palliativo. Oggi il salto di qualità è rappresentato dall'integrazione tra radioterapia e chemioterapia, che permette un aumento del controllo locale. Questa integrazione è importante per il fatto che la sopravvivenza a 5 anni dei tumori con istologia ad alto grado è circa del 50%. L'incidenza globale di metastasi è di circa il 25%. Le principali sedi di metastatizzazione sono polmoni, fegato, ossa, SNC ed altri organi. In caso di malattia metastatica, la chemioterapia riveste un ruolo meramente palliativo.

Palliative chemotherapy

In advanced stage or metastatic carcinomas of the salivary glands, there are few reports of cases being treated with a single chemotherapeutic agent [1]. Cisplatin is considered the most active drug and is the "backbone" of polychemotherapeutic regimes. In 1981-1982, an improvement in the response rate to cisplatin was reported, reaching 70%, in a series of study groups with fewer than 15 cases in each [2 3]. In 1991, Licitra reported a more realistic response rate of 16% in 25 consecutive cases [4].

In metastatic and relapsed disease, cisplatin, anthracycline, paclitaxel and vinorelbine are the most effective agents. Combinations associating cisplatin + anthracycline/vinorelbine are well tolerated. Combined regimes are, however, more toxic than the individual chemotherapy agents. Mean duration of complete response is between 7 and 18 months. Despite the lack of apparent benefit in terms of survival, decreased pain and control over local disease is often considerable.

The most commonly used regime in squamous cell carcinoma (SCC) of the head and neck, cisplatin + fluorouracil, has led to disappointing results in terms of objective response [5]. Taxol is effective above all in mucoepidermoid carcinomas and in adenocarcinomas [6]. Among the combinations, administration of carboplatin + taxol has, in our experience on 14 patients, resulted in 2 partial responses and 7 cases of stabilised disease [7]. The association of cisplatin, adriamycin and cyclophosphamide has a significant effect with a total response rate between 27% and 50% [8]. The protocol cisplatin, adriamycin or epirubicin and 5 fluorouracil has shown a total response rate between 37% and 47% [9], comparable to that of the cis-

platin + bleomycin + adriamycin/VP-16 combination [10].
Cisplatin and vinorelbine have synergic activity both *in vitro* and *in vivo*. In a randomised phase II study, 36 cases were randomised to treatment with vinorelbine alone versus the cisplatin + vinorelbine combination. In the combination group, there were 3 complete responses (19%) and 4 partial responses (25%), whereas with vinorelbine alone, there were only 4 partial responses (20%). Overall, median survival was 11 months in cases submitted to polychemotherapy versus 8.5 months in those undergoing monochemotherapy [11].

Neoadjuvant chemotherapy

Response to neoadjuvant chemotherapy can improve prognosis and increase the possibility of applying conservative treatment, but, in itself, does not appear to improve survival [12]. The response to neoadjuvant protocols might be significant in planning subsequent concomitant chemotherapy plus radiotherapy.

Adjuvant chemotherapy

Triozzi et al. used a polychemotherapy protocol consisting of vincristine + cyclophosphamide + fluorouracil in 14 patients with adenocystic carcinoma, following loco-regional treatment; these authors reported an effective reduction in metastases at follow-up versus a historic control group [13]. Other authors have reported that, in SCC of the head and neck, adjuvant chemotherapy remains an experimental approach, and overall survival is not improved [14].

Concomitant chemotherapy/radiotherapy

In locally advanced carcinomas of the head and neck, a recent meta-analysis showed a significant benefit with chemotherapy concomitant to radiotherapy versus radiotherapy alone [12].
Two recent randomised trials evaluated the administration of cisplatin plus conventional radiotherapy versus post-operative radiotherapy in patients with high risk of relapse. The clinical evolution was found to be improved in patients in the first group [15 16]. Airoldi et al. [17] tested the administration of cisplatin concomitant to conventional radiotherapy, followed by 3 adjuvant cycles with cisplatin + VP-16, in 6 patients with inoperable non-differentiated carcinoma of the parotid gland (T3-4 N0-1). Results using radiotherapy alone are not encouraging. This study reported complete remission in 50%, partial response in 33%, no response in 16%, and a median survival of 18 months [17]. These results indicate that chemotherapy may be an effective means to enhance radiotherapy.

New goals

Recent studies have evaluated the expression of molecular targets in carcinoma of the salivary glands. These drugs have achieved response rates between 6% and 20% and stable disease in 25-40% of cases.
C-kit is expressed in carcinomas of the salivary glands. This is a tyrosine kinase receptor which plays an important role in the development of haematopoietic cells, melanocytes and germ cells. Mutations at exons 11 and 17 produce activation of c-kit in some tumours (e.g. in 90% of adenocystic carcinomas) [18]. Inhibitors of anomalous c-kit tyrosine kinase have been identified (e.g. imatinib mesylate) and used in phase I and phase II trials in the treatment of chronic myeloid leukaemia and gastrointestinal stromal tumours. Evaluation of the clinical impact of imatinib mexilate in adenocystic carcinomas is of great interest, especially as it might be efficacious in the biologically more aggressive forms, with grading 3. Epidermal growth factor (EGF) is present in 20-85% of adenocystic carcinomas [19 20]. EGF is an important mediator of cell growth, cell differentiation and survival. Among the peptide growth factors, EGF/TGF_ (tumour growth factor alpha) are the chief endogenous ligands that determine EGF-mediated stimulation of tumour growth and progression, angiogenesis, cell survival and the metastatic process. Today, monoclonal antibodies are available that target EGF, and likewise potent inhibitors of specific EGF tyrosine kinase. P53 is an oncosuppressor gene involved in the carcinogenesis of the salivary glands. Its expression is associated with adenocarcinomas, pleomorphic adenomas, duct carcinomas, tumours at an advanced stage. Clinical trials are under way to study gene therapy using adenovirus-p53; through this viral vector, it is now possible to restore the "wild type" gene 53, obtaining an objective response in carcinomas of the head and neck.

Conclusions

Chemotherapy including cisplatin can enhance radiotherapy. The goal is to integrate radiotherapy and medical therapy in the treatment of inoperable tumours and in post-operative adjuvant therapy. Palliative therapy might benefit from the new biological drugs, to be used in association one with another or with traditional chemotherapy.
On account of the rarity of this disease, it is very difficult to perform randomised studies on large se-

ries; it is, therefore, very important to monitor phase II studies with particular care in order to determine the best treatment options and consolidate results.

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