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Editorial Review

Neoplastic chemotherapy and head and neck cancer

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Sulphur mustard was synthesized in 1854 and its vesicant properties described in 1887. Medical attention was focused on the chemical during World War I when its vesicant action on the skin, eyes and respiratory tract was noted in full and it was developed as a chemical weapon. It became apparent that those who survived gassing with sulphur mustard frequently developed leukopenia and in those that died, aplasia of the bone marrow was noted by Krumbhaar and Krumbhaar in 1919. Between World War I and II, nitrogen mustards were developed and much work was carried out by Gilman *et al.* (1963). Regrettably, early phases of research were carried out under the restrictions of military secrecy, but fortunately, at the end of World War II research could go on unabated and openly. Thus, the nitrogen mustards, the first successful chemotherapeutic agents, came into being.

Perhaps next most important historically was methotrexate. This is an antifolate drug and is very important as it produced the first striking, although temporary, remission in leukaemia (Farber *et al.,* 1948) and the first cure of a solid tumour (choriocarcinoma) (Hertz, 1963).

Drugs that have subsequently been found to be useful in head and neck squamous carcinomas and salivary tumours included 5-fluorouracil, methotrexate, bleomycin, mytomycin C, and cisplatin. Some studies have also included vincristine, cyclophosphamide and, the new agent taxol.

It is impossible to give a full account of chemotherapy of the head and neck region in a short article but the salient points will be discussed. Chemotherapy may be given alone with curative intent (very rarely successful in head and neck cancer). It may be given with palliation in mind or it may be given in combination with other modalities of treatment with an aim to cure the tumour. When administered with this intent there are various regimes. These are neo-adjuvant (before the other methods of treatment), adjuvant (at the same time as the other treatment), or as a radiation sensitizer (for instance, cisplatin and radical radiotherapy in combination).

According to Forastiere (1994) 20–30 per cent of all deaths from head and neck cancer occurred due to distant metastases and it was with a view to reducing distant metastases that most chemotherapy is given. Whilst chemotherapy in head and neck cancer has shown some impressive results in phase II studies, randomized trials that show convincing evidence of survival are extremely few. The most active single agents in head and neck chemotherapy are cisplatin, 5-fluorouracil, methotrexate, and bleomycin. Several other agents also have some activity. Response rates can be as high as 30–40 per cent but complete responses are uncommon. The duration of response is usually no more than six months. In an effort to improve the results of chemotherapy, combination therapy was evolved. Whilst increased response rates have been noted using this strategy, increased survival has not. Of the various studies that have been carried out on various agents, the most successful combination appears to be 5-fluorouracil and cisplatin. The overall response rate with this regimen is in the region of 33 per cent (Forastiere, 1994). Whilst cisplatin has considerable toxicity to the kidneys, cochlea and the blood-forming organ, much of the toxicity can be reduced by prehydration. The main problem with cisplatin is its ability to cause severe nausea and vomiting, although the new histamine H3 antagonists have reduced this problem very significantly. The main problem with 5-fluorouracil is that it causes mucositis. In 1992, Jacobs *et al.* compared 5-fluorouracil and cisplatin in combination and each on its own as a single agent. The response rate was better with the combination treatment but survival time for these end-stage patients was no different with a median survival of around six months.

In a complex study, the Liverpool Head and Neck Oncology Group headed by Philip Stell (1992) compared single agent cisplatin and methotrexate with the combination of cisplatin and 5-fluorouracil. Although there was no difference in response rate, the survival was significantly better in the cisplatin arm of the study, although there was still less than six months median survival.

Chemotherapy is one of those treatment modalities, like many others, that can make the patient worse rather than better. In an editorial by Philip Stell (1990) it was noted that adjuvant chemotherapy reduced cancer morbidity by three per cent. He found, by meta-analysis, that the death rate from toxicity from the agents he studied was 6.5 per cent. This shows an overall reduced survival from adju-

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vant chemotherapy of 3.5 per cent! Because of this, one must beware of using tumour-specific survival and response to treatment alone as a meaningful outcome measure of a regimen. This is particularly true when palliative treatment is being investigated. Here even the symptoms created by chemotherapy may make the treatment not worthwhile. There is no point making the patient's last few months miserable with no chance of cure. Browman and Cromin (1994) performed a meta-analysis of randomized trials of chemotherapy in recurrent disease and supported the conclusion that combination chemotherapy was better than single agent chemotherapy and there was a strong trend to suggest that cisplatin with 5-fluorouracil was the best combination. In spite of good response rates, the overall median survival was still only around six months. Regrettably, the authors showed that the cisplatin, 5-fluorouracil combination produces greater problems in nausea and vomiting, although as mentioned earlier, this should be alleviated by the newer H3 antagonists.

It rapidly became apparent that chemotherapy was very rarely curative in itself in squamous cell carcinoma of the head and neck. It was felt, however, that in conjunction with surgery and/or radiotherapy a treatment advantage may be attained.

The concept of combining chemotherapy and radiation is that chemotherapy has the potential to eradicate sub-clinical metastases and to reduce locoregional tumour bulk. Irradiation on the other hand, is mainly effective in dealing with low volume disease, therefore, the combination of treatments may be expected to be efficacious (Steel and Peckham, 1979).

In one large organ preservation series, The Department of Veterans Affairs Laryngeal Cancer Group (1991) carried out a randomized control trial of 332 patients with locally advanced laryngeal cancer. Half the group received surgery and post-operative radiotherapy and the other half received chemotherapy, the responders, in addition, receiving radical radiotherapy and the non-responders surgery and radiotherapy. The survival rate was similar in both arms of the study (nearly 70 per cent). This result is a little surprising as the chemotherapy group demonstrated fewer distant metastases, which is considered as one of the main killers in head and neck cancer.

One of the problems in chemotherapy is delivering the drug to the tumour. One way of improving drug delivery is by intra-arterial injection into the tumour's blood supply. Regrettably, this has been associated with high complication rates (Arcangeli, 1983).

As mentioned above, the Veterans study compares surgery and radiotherapy with chemotherapy and radiotherapy. Chemotherapy and radiotherapy given together, as previously mentioned, should offer advantages over either modality alone. Certain drugs are known to be radiosensitizing, these include 5-fluorouracil, mytomycim, cisplatin, carboplatin, hydroxyurea and paclitaxel. Two types of clinical trials have been carried out; using chemo-radiation. The first is with chemotherapy added to standard radiotherapy, with no modification to the radiotherapy. Here, the chemotherapy is frequently a single agent given at low to moderate doses with radiosensitization as the goal. The second approach uses chemotherapy administered in full doses, both to sensitize and also kill cells. This results in considerably increased toxicity and requires interruption of treatment to allow normal tissue to recover. Interrupting radiotherapy is a potentially bad concept as it gives tumour cells a chance to proliferate. In the case of chemoradiation however, the drug may be expected to stop repopulation of the cells when radiotherapy is not being administered (Tannock, 1995). Toxicity is increased using two modalities of treatment and in one trial, the incidence of mucositis, which was severe in the radiation field, rose from nine per cent to 21 per cent in those patients receiving concurrent methotrexate (100 mg per m^2) (Gupta *et al.*, 1987). In addition, bone marrow toxicity may become a problem and make the mucositis much worse and potentially life-threatening.

In spite of these potential problems, six trials combining low dose chemotherapy with radiation have shown an improvement in local control and have even shown a trend in improved survival. This is particularly true for the oral cavity and oropharynx (Lo, 1976; Gupta *et al.*, 1987). In a meta-analysis of 16 randomized trials, Munro (1995) demonstrated that single agent chemotherapy with radiation improved survival by about 12 per cent. Cisplatin appears to be the most effective single agent and has been shown to reduce repair of radiation-induced damage (Dewitt, 1987). Bachaud *et al.* (1991) gave cisplatin at a dose of 50 mg m^2 administered weekly, with post-operative radiotherapy. Whilst only between half and two thirds of patients received scheduled chemotherapy, local control and survival were improved. Glicksman *et al.* (1994) gave cisplatin by continuous infusion on days 1 and 4 and 22–25 during pre-operative radiation therapy. Twenty-two patients with Stage 3 and Stage 4 disease had a pathological complete remission of the disease at surgery. These patients went on to have post-operative irradiation at 27 Gy with cisplatin on days 1 and 4. The disease-specific survival was encouraging at 78 per cent at three years. This trial suggests that continuous cisplatin infusion may be necessary ensuring the drug is present at the time of radiation, although the toxicity from such regimes is quite high, it does appear acceptable. Merlano *et al.* (1992) combines cisplatin and 5-fluorouracil alternating with radiotherapy at a dose of 60 Gy. The median survival was 41 per cent in the combined treatment group compared with 23 per cent in the radiotherapy alone group, the difference in survival was attributed to an improvement in locoregional control.

It would be prudent here to give an overview of the various trials that have been carried out in head and neck cancer. Arcangeli (1983) using intra-arterial methotrexate as the adjuvant treatment

found an improved survival with chemotherapy ($p<0.05$). Kun (1986) found a poor survival with a very complex chemotherapy regime of bleomycin, cyclophosphamide, methotrexate and 5-fluorouracil. Such complex regimes should probably not be used. The Head and Neck Contracts Programme (1987) used cisplatin and bleomycin as the adjuvant treatment and did find a survival benefit. Schuller *et al.* (1988) using a combination of adjuvant chemotherapy agents found no difference in survival and nor did Gehanno *et al.* (1992) using carboplatin and 5-fluorouracil. A similar lack of improved results were noted by Paccagnella *et al.* (1994) using cyclophosphamide and 5-fluorouracil, distant metastases were, however, decreased. Randomized trials using concomitant chemotherapy and radiotherapy frequently do show an increased survival in the chemotherapy arm compared with the radiotherapy arm alone. Typical results are 18 per cent improved to 49 per cent at two years in the chemotherapy arm (Lo *et al.*, 1976); 17 per cent improved to 72 per cent at five years (Shanta and Krishnamurti, 1980); 15 per cent to 31 per cent at three years (Fu *et al.*, 1987); (Weissberg *et al.* 1989) 55 per cent to 75 per cent at 55 years and (Bachaud *et al.*, 1991) from 41 per cent to 65 per cent at two years. These studies all use single agent treatment, either 5-fluorouracil, bleomycin or cisplatin. Against these good results should be noted a study by Browman and Cromin (1994) who, using 5-fluorouracil noted no improvement in survival in the chemotherapy arm and Eschwege *et al.* in the EORTC study (1988) using bleomycin.

Conclusion

The evidence presented from randomized trials shows that response rates from neoadjuvent chemotherapy show some promise but long-term survival differences are small. It should also be noted that patient compliance with these relatively complex therapies tends to be reduced. Nevertheless, several trials have shown a reduction in distance metastases in the chemotherapy arm and this is obviously encouraging. Concomitant chemoradiation seems particularly promising, the optimum drug and dosage of that drug still requires further elucidation by clinical trials, as does the dose and timing of radiation. In all such trials it should be noted that toxicity must be well documented.

It seems likely that neo-adjuvant chemotherapy, particularly with radiation, as well as perhaps in patients also treated by surgery will become standard practice.

At present, chemotherapy, no matter how it is delivered and in what regime, should probably only be given in centres where trials are under way. Exceptions to this rule would be when the drugs are used in palliation, or rarely perhaps, as a method of downstaging otherwise inoperable and untreatable tumours in young patients.

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