Morbidity of combined chemotherapy and radiotherapy

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Introduction
Combining radiation with systemic therapy has been increasingly used for multiple tumour sites in an attempt to improve tumour control probability (TCP). There are many ways in which they can be combined, but in general these can be divided into delivery of the systemic therapy before (neoadjuvant), during (concurrent) or after (adjuvant) radiation.

Although a little simplistic, adjuvant therapy is generally used with the hope of basic additive anti-tumour effects with the radiation eradicating the primary site and the systemic therapy administered to control metastatic spread. Neoadjuvant therapy can supplement this with a reduction in volume of the primary site possibly rendering it more amenable to local control by radiotherapy. The morbidity of these approaches is reasonably predictable, simply combining the normal side effects of each modality.

This article will concentrate on concurrent treatment as this has the potential for enhanced anti-tumour efficacy beyond the additive effects of each individual modality.

The strategy of concurrent treatment
Although the reason for combining systemic therapy and radiotherapy in a concurrent fashion may be simply to achieve therapeutic gain by additive independent cell kill, their delivery at the same time also allows for the possibility of true drug-radiation interaction (radiosensitisation) to enhance anti-tumour efficacy. A significant increase in local toxicity within the radiotherapy field would be anticipated as well as increased systemic morbidity which can result in long-term problems for patients (see figure 1).

Therapeutic gain can only be achieved if the additional side effects of the combination do not outweigh the improvement in TCP. Unfortunately, most published studies tend to concentrate on the effects on acute toxicity and there is more limited information on the late effects of combination treatment.

Cytotoxic chemotherapy
Laboratory studies have shown that a number of drugs, including actinomycin D, doxorubicin, cisplatin and cyclophosphamide enhance radiation effects to varying degrees in different normal tissues like skin, lung, bladder, oesophagus and intestine, with heamatopoietic tissue especially susceptible. The effects vary considerably depending on the timing of drug delivery and whether single or multiple fractions of radiation are used. This provides laboratory evidence to support the clinical outcomes observed in studies of these drugs in a number of tumour sites, but also a degree of prediction of the potential normal tissue side effects experienced by patients.

FIGURE 1
The potential consequences of multi-modality therapy. 52-year-old man with locally advanced cancer of the floor of mouth treated with surgery followed by adjuvant chemoradiotherapy. Three months after completion of treatment, he developed a severe flexion deformity of the neck secondary to loss of neck extensor function and anterior skin fibrosis. Hard collar proved ineffective as it produced pressure necrosis. Eighteen months post-treatment he remains disease-free but with poor QoL as a result of this non-specific but severe morbidity.

In head and neck squamous cell cancer (HNSCC), a large meta analysis and its follow-up have confirmed the overall survival benefit of concomitant platinum chemotherapy with radiation but within the treatment fields, as might be anticipated, there is a near doubling of the rate of grade 3 and 4 mucositis which renders this combination very toxic. Interestingly, the benefits of treatment reduce with age, and are lost above 70 years, with cancer specific deaths reducing with advancing age. This clearly demonstrates the additional burden to patients of combined modality therapy with proportionately more elderly patients succumbing to non-cancer causes of death.

In the CNS, an EORTC phase 3 study comparing radiotherapy to chemoradiotherapy (concomitant and adjuvant temozolomide) has shown a significant improvement in median survival (12.1 to 14.6 months) and two-year survival (10.4% to 26.5%). Although the health-related quality of life (QoL) data suggested this came at no QoL cost, since the introduction of chemoradiotherapy as standard, there has been an appreciation of a severe inflammatory/necrotic local reaction experienced by a significant proportion of patients within the high-dose radiotherapy field. Given this is radiologically indistinguishable from disease, the appearances are termed pseudoprogression, are present in ~40% of patients after radiotherapy and often require steroids to control the intracranial pressure, thus adding to the morbidity of treatment.

In oesophageal cancer, Herskovic et al compared radical radiotherapy alone with concurrent and adjuvant treatment with cisplatin and 5-fluorouracil. To compensate for the anticipated additional toxicity of the combination therapy, the radiation dose was reduced from 64Gy to 50Gy in the combined arm. Once more, and despite this reduction in...
Due to the potentially limited additional side effects, other tumour sites have been completed or are under way, figure 2 (27% versus 0%) to achieve the improved outcome demonstrated in the increase in morbidity is nevertheless felt to be acceptable despite the dreadful prognosis with single modality therapy, the field, with higher rates of severe oesophagitis. Given the歹大foul prognosis with single modality therapy, the increase in morbidity is nevertheless felt to be acceptable to achieve the improved outcome demonstrated in the longer-term follow-up of these patients (five-year survival of 27% versus 0%) though clearly restricts chemoradiotherapy to only the fittest patients.

A recently updated Cochrane review of trials of chemoradiation therapy in non-small cell lung cancer has shown the benefit of combined modality therapy using platinum, but in addition compared concurrent with sequential therapy, suggesting that concurrent treatment is superior. This review also reported on morbidity, with patients suffering more grade 3 and 4 oesophagitis as well as neutropaenia and anaemia with combined therapy; in addition, morbidity was enhanced in the concurrent over the sequential patients. Although there was better reporting of acute toxicities, long-term side effects were reported in a few studies with no apparent statistical difference in rates of pulmonary fibrosis and late oesophageal damage.

These examples demonstrate that chemoradiotherapy can result in improvement in TCP, but inevitably comes at the cost of increased toxicity, especially within the radiation treatment fields, thus adding significantly to the morbidity of radical therapy. Most of this toxicity appears to be concentrated on acute effects, but limits the benefits of this combination approach to only the fittest of patients.

Simply put, the more therapy delivered, the more toxicity results. Balancing this and trying to estimate which patients will derive the benefit and tolerate the morbidity is vital. Patients must be made aware of the potential long-term consequences of these morbidities, including persistent nasogastric feeding in head and neck cancer, or repeated endoscopic dilatations after severe oesophagitis in oesophageal cancer. The absolute benefits from chemotherapy may be small (~8% in HNSCC), thus it is important to discuss this fully with patients to ensure they understand the relative benefits and anticipated risks and give informed consent to the combination. In addition, although some of these morbidities can be easily predicted and discussed, the reasons for the age-related loss of benefit in HNSCC is more difficult to assess and great caution is warranted in considering elderly patients for combined modality therapy regardless of apparent fitness.

Other systemic agents
As biological agents in advanced cancer have demonstrated relatively mild side effects, these appear an attractive therapeutic option to combine with radiation. A phase 3 study in HNSCC comparing radiotherapy alone or in combination with concurrent cetuximab (an epidermal growth factor receptor inhibitor) resulted in a gain in overall survival at two and three years (46% vs 37% and 42% vs 31%, p<0.04 at three years). Despite concerns over potentially severe toxicity to skin and mucous membranes with an agent influencing epidermal surfaces, this was not observed in the study: Grade 3-5 mucositis 52% (XRT alone) vs 56% (with cetuximab) and radiation dermatitis 18% vs 23%. The use of this combination outside a clinical trial setting has been reported as showing much more severe skin toxicity and mucositis within the radiation field, thus there has been some doubt cast as to the relative benefits of this approach.

A number of early studies using biological therapy in other tumour sites have been completed or are under way, due to the potentially limited additional side effects, but much work remains to be done with these promising agents.

Radiotherapy strategies to limit morbidity
Modern radiotherapy planning and delivery systems, including intensity-modulated radiotherapy (IMRT) and velocity-modulated arc therapy (VMAT), have been proven to reduce the toxicity of radiotherapy in HNSCC due to improved conformity to tumour, with reduced normal tissue exposed to the high dose radiation field. These systems allow “dose-painting” of anatomical regions to receive specific doses, including sparing of normal tissue. Combining such strategies with the enhanced toxicity engendered by systemic therapy may allow some limitation of this increase and improve the therapeutic ratio as a result. The largely experimental technique of adaptive planning in which the radiotherapy field is reduced through the course of treat-
ment to compensate for a responding and thus shrinking tumour will also result in reduced radiation exposure of normal tissue, and presumably side effects as a consequence.

There may well be an expanding role, therefore, for modern delivery systems in limiting the observed toxicity of combined modality therapy opening it up to a wider proportion of patients.

**Summary**
Combining radiation and systemic therapy has become standard-of-care in many tumour sites due to the improvement in TCP, but always at a resultant increase in morbidity, especially within the radiation field. It seems unlikely that cytotoxic combinations can be adapted to make these strategies significantly safer and more available to less fit cancer patients, thus the use of more biological therapies may prove increasingly important over time. However, the lessons from cetuximab in head and neck cancer suggest that adding any therapy to radiation significantly increases the burden of morbidity for patients and those suitable will continue to require careful selection to maintain the therapeutic ratio.

**References**