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Original Article

The rationale for and the current role of chemoradiotherapy

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Abstract

Combined-modality treatment using chemotherapy and radiotherapy, particularly concurrently, has now become the standard of care for many solid tumour sites on the basis of improvements in locoregional disease control and in some cases survival. The rationale for combined-modality treatment, potential mechanisms of interaction, the therapeutic ratio and the current place of sequential and concurrent chemoradiotherapy are discussed.

Keywords

Chemotherapy; radiotherapy; chemoradiotherapy; interaction; rationale

INTRODUCTION

Radiotherapy is a major treatment modality used with curative intent for regionally confined malignant disease. It allows organ preservation in some tumour sites. Local and metastatic failure, however, remains a common occurrence, particularly for advanced disease. Different approaches have been tried to reduce local and metastatic failure. Radiotherapy techniques, including brachytherapy, intensity-modulated radiotherapy, proton therapy and stereotactic treatment, have been employed to improve the tumour control by allowing dose escalation to the tumour without an increase in normal tissue toxicity. An alternative and potentially complementary strategy is to attempt to manipulate the response to radiotherapy using either altered fractionation schedules or a combination of radiotherapy and systemic treatment. Combined-modality treatment using chemotherapy and radiotherapy, particularly concurrently, has now become the standard of care for many solid tumour sites on the basis of improvements in locoregional disease control and in some cases overall survival.[1–8]

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RATIONALE FOR COMBINED-MODALITY TREATMENT AND MECHANISMS OF INTERACTION

The combination of chemotherapy with radiotherapy may improve patient outcome by improving locoregional tumour control and/or by eliminating distant metastases. The classical framework for describing the possible interactions between chemotherapy and radiotherapy was defined by Steele.[9] Mechanisms including spatial cooperation and additive cell kill do not assume any direct interaction between the two modalities of treatment and can result only in additive improvement in tumour response. An enhanced, radiosensitising or synergistic interaction produces a treatment effect greater than the sum of the single modality treatments. In most clinical scenarios the mechanisms underlying the enhancement of radiation by chemotherapy

may be multiple and are only partially understood. Mechanisms leading to radiosensitisation are likely to vary with drug, schedule of drug administration and tumour type.

Spatial cooperation

Spatial cooperation occurs when the different treatment modalities target disease at different anatomical sites – in particular localised disease with radiotherapy and distant micrometastatic disease with chemotherapy. No direct interaction between chemotherapy and radiotherapy is required, although the toxicity profile must allow both modalities to be used at therapeutic dosages. The benefit of this approach is limited by the poor efficacy of systemic treatment at eliminating even subclinical metastases of adult solid tumours. Examples of effective spatial cooperation include the use of radiotherapy to treat chemotherapy sanctuary sites, such as prophylactic cranial irradiation in the treatment of small cell lung cancer.

Additive or independent cell kill

Tumour cell kill by chemotherapy can reduce the number of tumour clonogens that must be eradicated by radiotherapy to achieve tumour control. A non-overlapping spectrum of potential toxicity with each treatment modality allows an improved tumour outcome without an increase in the severity of normal tissue toxicity. Virtually all chemotherapy drugs, however, also show some increase in radiation damage to normal tissues.

Mechanisms of enhancement of radiotherapy response by chemotherapy

There are several ways in which chemotherapy and radiation may interact to increase tumour response.

Increased initial radiation damage

Initial radiation-induced cell death can be directly enhanced by the incorporation of drugs into DNA. For example, cisplatin can induce intra- and inter-strand DNA cross-links[10] and fluoropymidines such as 5-fluorouracil (5-FU) can be incorporated into DNA.[11]

Chemotherapy-mediated inhibition of cellular repair

Sublethal DNA damage induced by radiation can be repaired. The degree of successful repair is thought to play a critical role in the degree of cell death induced by radiotherapy in both the lethal/potentially lethal damage model[12] and the repair saturation model.[13] Several chemotherapy drugs, including fluropyrimidines,[11] cisplatin[10] and gemcitabine,[14] interfere with cellular repair processes and enhance radiation-induced DNA damage.

Effect of chemotherapy on hypoxic cells

As solid tumours grow, they develop their own blood supply through angiogenesis. This vasculature is, however, primitive, and parts of the tumour are poorly oxygenated. Oxygen plays a key role in the radiation response of tumours. Hypoxic cells are up to three times more resistant to radiation than oxygenated cells[15] and are a potential cause of local failure of radiotherapy. Chemotherapy can eliminate cells in well-oxygenated areas of tumour, leading to increased perfusion, re-oxygenation and hence increased radiosensitivity of previously hypoxic areas. Bioreductive chemotherapy drugs, such as mitomycin C, are reduced to toxic metabolites in a hypoxic environment and therefore have a degree of selective toxicity to the radioresistant hypoxic cells. Some compounds, such as nitroimidazoles, mimic oxygen and radiosensitise hypoxic cells. The use of the most potent nitroimidazole, misonidazole, is limited by neurotoxicity. Nimorazole is a less potent radiosensitiser but also less toxic and has demonstrated a significant benefit in local control in a radiotherapy trial of supraglottic and pharyngeal cancer (DAHANCA 5).[16]

Tumours contain areas of both acutely and chronically hypoxic cells.[17] Nicotinamide is a drug that appears to prevent transient fluctuations in blood flow within tumours and can therefore reduce acute tumour hypoxia, thus increasing radiosensitivity.[18] Nicotinamide is now being used in the ARCON (Accelerated Radiation, Carbogen and Nicotinamide) trials as part of a strategy to reduce hypoxia.

Repopulation

In preclinical studies, irradiated tumours proliferate more quickly than non-irradiated tumours.[19] Accelerated repopulation is beneficial to normal tissue recovery but detrimental

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to tumour control. Increased overall treatment time allows more repopulation and has been established to be an important factor for local failure for tumour types, including head and neck, cervix, non-small cell lung and oesophagus cancers.[20] Chemotherapy is generally more active against proliferating cells and can decrease repopulation when given concurrently with radiation. A therapeutic gain occurs if the tumour is repopulating faster than normal tissue or if the chemotherapy has a degree of tumour selectivity.

Cell cycle

Concurrent chemotherapy may act via cell cycle redistribution to enhance the effect of radiotherapy either by eliminating cells in radioresistant phases of the cell cycle, or by causing cells to accumulate in radiosensitive phases. Chemotherapy drugs such as gemcitabine preferentially eliminate cells in the radioresistant S phase.[21] In contrast, taxanes are mitotic spindle inhibitors that cause cells to accumulate in the radiosensitive G_2M phase.[22]

THERAPEUTIC GAIN

Any strategy designed to improve the outcome of radiotherapy must be not exceed normal tissue tolerance. The addition of systemic treatment to radiotherapy has the potential to increase normal tissue toxicity in terms of both the severity of expected radiation-induced toxicity and the possibility of a wider spectrum of toxicity. A therapeutic gain is achieved if the increase in tumour control is greater than any increase in normal tissue toxicity. In trials in which the addition of chemotherapy to radiotherapy results in improved tumour control with increased toxicity, it can be difficult to ascertain whether this represents a true therapeutic gain. The classical normal tissue tolerances used in radiotherapy[23] are based on the delivery of radiotherapy as single-modality treatment, and data for combined-modality treatment are less well established. With combined-modality treatment, the likely detrimental effect on normal tissue tolerances must be taken into account, and a reduced radiotherapy dose may be considered to avoid exceeding normal tissue tolerance.

THE SEQUENCING OF CHEMOTHERAPY AND RADIOTHERAPY

Neoadjuvant or induction chemotherapy has been used in an attempt to gain the benefit of full therapeutic doses of chemotherapy using spatial cooperation and additive cell kill, without the enhanced toxicity of concurrent treatment. Although induction chemotherapy can produce tumour shrinkage, benefit in terms of local control and survival has been generally disappointing. However, there is now emerging evidence of limited benefit for some tumour sites, including lung, bladder and head and neck tumours.[5,24,25] The benefit of sequential treatment may be limited by accelerated repopulation and prolonged overall treatment time. Changes in the tumour microenviroment, including reoxygenation, may occur following response to chemotherapy, stimulating accelerated repopulation at the time of commencement of radiotherapy.[26]

The use of concurrent chemoradiotherapy avoids the prolonging of overall treatment time and has had promising result in terms of local control and overall survival for many tumour sites. The true degree of therapeutic gain for many of these recently introduced regimens cannot yet be fully assessed, as the extent of late toxicity has not been fully realised.

CHOICE OF CHEMOTHERAPY DRUG AND SCHEDULE FOR COMBINED-MODALITY TREATMENT

Drugs used in combination with radiotherapy are generally chosen because of their known activity in a particular disease site. Cisplatin is one of the drugs most commonly used in combination with radiotherapy, with multiple potential mechanisms of interaction, including fixation of repairable damage, cell cycle effects and inhibition of repair.[10] Another drug that is widely combined with radiotherapy is 5-FU, with the mechanism of interaction involving the killing of radioresistant S-phase cells and cell cycle dysregulation.[10] Capecitabine is an

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oral prodrug whose metabolites are converted to active 5-FU. Capecitabine is of interest because it is an oral medication that aims to mimic the continuous infusion of 5-FU needed to ensure consistent tissue levels of the drug during the delivery of each radiotherapy fraction.

The interaction of drugs and radiotherapy is dependent upon dose and temporal relationship. Different regimens of drug administration have been developed for different tumour sites. These have usually come from knowledge of drug schedules used when chemotherapy is given as single-modality treatment and from the results of early clinical trials, as opposed to coming from knowledge of chemotherapy–radiation interactions. Chemotherapy dose escalation is not necessarily beneficial and may not enhance radiosensitisation.[10] As the mechanism of interaction is clarified, it may be possible to improve current schedules of drug delivery and to determine whether single or multiple drugs should be combined with radiotherapy to optimise radiosensitisation.

NOVEL AGENTS

The identification of molecular defects in malignant cells has stimulated the development of targeted drug therapies. Targeting specific tumour defects has the advantage of avoiding the normal tissue toxicity seen with conventional cytotoxic chemotherapeutic agents. There is evidence of a possible radiosensitising effect of drugs directed at various targets, including cell cycling, angiogenesis and signal transduction.[27] A combination of targeted therapy and radiotherapy holds the promise of improving the therapeutic index through increased tumour cell kill with minimisation of normal tissue toxicity.

CURRENT ROLE OF CHEMORADIOTHERAPY

Brain tumours

Glioblastoma multiforme, the most common primary brain tumour in adults, is incurable and is associated with a dismal prognosis, with a median survival of less than 12 months.[28] Radiotherapy after surgery offers improved survival compared with best supportive care.[28] Until recently, chemotherapy, with the limitation of restricted access to the tumour via the blood–brain barrier, had only been shown to be of minimal benefit. A Phase III trial by the European Organisation for Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) has now demonstrated substantially improved survival with the administration of oral temozolomide, an alkylating drug, concurrently with radiotherapy and then alone as maintenance treatment.[1] Median survival was 14.6 versus 12.1 months, and 2-year survival rate was 26% versus 10%, favouring the combined modality. This benefit was significant only for patients with a WHO performance status of 0 or 1. It is not possible to distinguish the relative benefits of the concurrent chemoradiotherapy and maintenance chemotherapy components of the treatment.

Head and neck tumours

Induction chemotherapy has been an attractive strategy for patients with locoregionally advanced head and neck cancer, with response rates of more than 70% for regimens such as cisplatin and 5-FU.[25] Despite this, minimal benefit was seen in terms of local control or overall survival.[2] Induction chemotherapy has been used to select responders who are suitable for an organ-conserving treatment.[29] With improvements in locoregional therapy, the development of distant metastases has become an increasing problem. New multi-agent induction chemotherapy regimens, including taxanes, have been shown to have some promise[25] and are likely to play an increasing role as distant failure becomes more common. Concurrent chemoradiotherapy strategies have proven more effective. A meta-analysis of 63 trials (10,741 patients) of locoregional treatment with or without chemotherapy demonstrated minimal survival impact of neoadjuvant or adjuvant chemotherapy, but an 8% absolute survival benefit of concurrent chemoradiotherapy at 5 years.[2] Concurrent treatment with single-agent cisplatin is now in routine use in unresectable disease, in high-risk post-operative patients,[30] as an organ conservation strategy[31]

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and in the treatment of nasopharyngeal cancer.[32] Recently, the monoclonal antibody cetuximab, targeted against epidermal growth factor receptor has been combined with radiotherapy with improved local control and survival compared with radiotherapy alone. Importantly, no increase in the main radiotherapy side effects was observed.[33]

Oesophagus

Potentially curative treatment approaches for localised disease include surgery, radiotherapy and chemoradiotherapy. Chemoradiotherapy offers a substantial improvement in outcome compared with radiotherapy alone. In the intergroup study concurrent chemoradiotherapy with cisplatin and 5-FU achieved a 5-year survival (26% versus 0%) compared with radiotherapy alone, at the cost of increased toxicity.[3] Surgery and chemoradiotherapy have not been directly compared in the radical treatment of oesophagus cancer and comparison of series is difficult owing to differing patient selection, with patients treated by surgery tending to be at an earlier stage of disease. Chemoradiotherapy is, however, likely to offer cure rates similar to surgery. Pre-operative chemoradiotherapy has been the subject of several studies but has not demonstrated any consistent benefit. Treatment decisions are individualised based upon site of tumour, comorbidity, swallowing function and patient preference. In general, chemoradiotherapy is preferred for tumours of the upper-third region of the oesophagus and surgery for tumours of the lower-third oesophagus, where surgical access is easier.

Small cell lung cancer

Sequential chemotherapy and radiotherapy for limited-stage small cell lung cancer offers an absolute survival benefit of 5% compared with chemotherapy alone.[4] Some data suggest that the time from start of chemotherapy to completion of radiotherapy is a key variable in predicting outcome.[34] The optimal sequencing of treatment appears to be concurrent.[35,36] The Japanese Clinical Oncology Group Study[35] is the only randomised trial comparing sequential chemoradiotherapy with concurrent chemoradiotherapy. The 5-year survival rate of 23.7% versus 18.3% favouring concurrent treatment (non-statistically significant) is consistent with the impressive 26% reported in the twice-daily fractionation arm of Turrisi et al.'s concurrent chemoradiotherapy study.[37]

Non-small cell lung cancer

Locally advanced lung cancer (stage III) is usually considered unresectable. The outcome with radiotherapy alone is very poor, and attempts have been made to improve the outcome with combined-modality non-surgical treatment. Randomised trials and meta-analysis have demonstrated improved survival with the use of sequential chemotherapy and radiotherapy for this group.[5] In one influential meta-analysis, the addition of chemotherapy provided an absolute survival gain of 4% at 2 years.[38] Four phase III studies have compared a sequential approach with concurrent treatment.[39–42] These have favoured a concurrent approach, with improved median survival in the order of 2–4 months, at the cost of increased oesophagitis. Results of ongoing UK trials of concurrent treatment in both early and advanced stages of non-small cell lung cancer are awaited.

Rectum

There is now strong evidence for the superiority of 5-FU-based chemoradiotherapy compared with long-course radiotherapy alone preoperatively in the treatment of resectable rectal cancer. The EORTC 22921 trial of 1,011 patients[6] demonstrated a local recurrence rate of 9% with pre-operative chemoradiotherapy, compared with 17% with long-course radiotherapy. Similarly, the FFCD 9203 study of 733 patients[43] showed an approximate halving of local recurrence from 16.5 to 8% with chemoradiotherapy, compared again with long-course radiotherapy. In neither trial was there any impact upon overall survival. A German study showed reduced local recurrence (6% versus 13%) and reduced acute and late toxicities, favouring preoperative as opposed to post-operative chemoradiotherapy.[44] There is considerable variation internationally in the selection of patients and timing of chemoradiotherapy. Preoperative chemoradiotherapy is used to

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produce tumour regression to facilitate a clear circumferential resection margin. In the UK, it is mainly used when the tumour threatens the mesorectal fascia or in low rectal cancer with a high risk of an involved circumferential resection margin.[45] 'Standard' chemoradiotherapy has used fluropyrimidines. There is considerable interest in attempting to incorporate a second drug (oxaliplatin or irinotecan) into the regimen, with some encouraging early data showing increased pathological response rates[45].

Anal cancer

The initial studies of Nigro[46] demonstrated impressive rates of local control using approximately 30 Gy of irradiation with concurrent administration of mitomycin and 5-FU. Three phase III trials have looked at combining radiation with 5-FU and mitomycin. The UKCCCR[7] and EORTC[47] studies compared concurrent chemoradiotherapy with radiotherapy alone, demonstrating improved local control (61% versus 39% in the UKCCCR trial at 3 years and 68% versus 55% at 3 years in the EORTC trial) and colostomy-free survival with chemoradiotherapy. The RTOG study[48] demonstrated the advantage of adding two courses of mitomycin to 5-FU and radiotherapy. The current standard is, therefore, a combination of 5-FU and mitomycin with radiotherapy for epidermoid anal cancer, reserving surgery for failures.

Cervix

Two meta-analyses have demonstrated the superiority of chemoradiotherapy over radiotherapy alone for cervical carcinoma.[8,49] Green et al.'s meta-analysis showed a hazard ratio of 0.71 (95% CI 0.63–0.81) and an absolute benefit of 12% for overall survival in favour of combined-modality treatment.[8] Lukka's analysis similarly showed a risk reduction of death of 0.74.[49] Chemoradiotherapy with concurrent cisplatin is now the standard of care for cervical carcinomas of bulky stage 1B and above.

Bladder

Meta-analysis of the role of neoadjuvant chemotherapy has demonstrated an absolute benefit in overall survival at 5 years of 5% with cisplatin-based regimens, regardless of the form of local treatment, for invasive bladder cancer.[24] Some series have supported a potential role of concurrent treatment in an organ-preserving approach,[50] although this approach is largely confined to the trial setting at present.

DETRIMENTAL INTERACTIONS BETWEEN CHEMOTHERAPY AND RADIOTHERAPY AND RADIATION RECALL

As discussed, chemotherapy and radiotherapy are often combined, with the aim of improving the therapeutic ratio. However, any interaction with the potential to increase toxicity may be undesirable, particularly in less fit patients or in palliative treatment regimens. In these circumstances, caution is required to avoid significant additive toxicity or enhancement of toxicity when chemotherapy and radiotherapy are administered in close proximity. For example, palliative chemotherapy followed by palliative pelvic radiotherapy can cause excess bowel toxicity as a result of overlapping toxicity profiles, unless a suitable interval is allowed between treatment modalities. Treatment scheduling needs to be individualised to allow adequate recovery following each treatment modality, but balanced with the need to obtain optimum palliative benefit. Particular care is required with drugs that are potent radiosensitisers.

The interaction between chemotherapy and radiotherapy can be unexpectedly detrimental. When radiation is followed by chemotherapy, subclinical damage resulting from irradiation can be unmasked, producing an inflammatory reaction in a previously irradiated site, termed 'radiation recall'. This phenomenon is most commonly reported in the skin but can also occur in other organs.[51] The mechanism of 'radiation recall' is unclear. One possible explanation is that the stem cell pool in the treated field is depleted by radiotherapy, and subsequent chemotherapy leads to further stem cell death, resulting in earlier senescence in remaining cells.[52] An alternative theory is that mutations induced in cells surviving irradiation may render them, or their progeny, incapable of

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normal proliferation, leading to an enhanced response to later chemotherapy.[53]

TREATMENT OF ELDERLY/ COMORBID PATIENTS

The trials testing concurrent approaches to treatment do not generally include less fit and more elderly patients. This group of patients is more susceptible to the increased toxicity of multimodality treatment. The potential to obtain small proportional improvements in disease control makes combination treatment regimens more difficult to justify in less fit or elderly patients in the face of the likelihood of increased toxicity. In these situations, treatment needs to be individualised and may involve modified concurrent, sequential or single-modality treatment.

CONCLUSION

The combination of chemotherapy and radiotherapy has become commonplace in the treatment of most solid cancers, with concurrent use providing significant improvements in locoregional control and overall survival. These gains are, however, small for some tumour sites, and the long-term outcome often remains poor. Combination treatment is associated with increased toxicity, and data on quality of life are limited. The selection of fitter patients in terms of age and performance status for combination treatment is important to improve disease control while avoiding excessive treatment-induced morbidity. In the future, an improved understanding of the mechanisms of interaction of combined-modality treatment and the incorporation of novel agents hold the promise of improving the therapeutic ratio.

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