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The combined use of radiotherapy and chemotherapy in the treatment of solid tumours

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Abstract

Several clinical trials carried out during the last decade clearly show that concomitant radiotherapy and chemotherapy significantly improves local control in a variety of advanced solid tumours. In most of these trials, cisplatin alone or in combination with other drugs has been used. This has led to improved survival rates in head and neck, lung and cervical cancer. The interaction of radiotherapy with chemotherapy for these solid tumours appears to be schedule-dependent, as no such an improvement was observed with neo-adjuvant chemotherapy followed by radiotherapy in eight out of nine clinical trials in cervical cancer. A major advantage of this combined modality treatment is organ preservation possible for patients with advanced larynx or anal cancer. Major further improvement can be expected from the design and exploration of drugs that influence the pathways leading to cell death after irradiation. Examples include topoisomerase 1 (topo1) inhibitors, alkyl-lysophospholipids, epidermal growth factor receptor (EGFR) receptor inhibitors.

Keywords: Chemotherapy; Radiotherapy; Translational research

1. Introduction

The combination of radiotherapy and chemotherapy is an appealing approach that has led to improved treatment results in patients with advanced solid tumours. This has been demonstrated in several clinical trials during the last decade. In particular, the concomitant use of radiotherapy and chemotherapy resulted in a lower recurrence rate and improved survival of loco-regional tumour of relative risk (RR) of death in several sites, such as head and neck [1], lung [2], and cervix [3]. The scheduling of radiotherapy and chemotherapy appears to be critical. Less or even no improvement in the treatment results was reached when chemotherapy was given before or after radiotherapy [4,5]. A major advantage of the combined treatment is the possibility to obtain a higher organ-preservation rate. Examples are sparing of the larynx or anus (by applying this combined treatment) in patients with advanced head and neck [6] or anal cancer [7]. These benefits clearly outweigh the often-observed increased acute toxicity of combined radiotherapy and chemotherapy. Unexpectedly, hardly any or only a limited increase of severe late side-effects has been reported up to now. These improved treatment results stimulate further exploration of combined modality treatments, as there are still too many loco-regional recurrences, for which curative salvage treatment is often not possible. Further improvement can be obtained by a better selection of drugs on the basis of their mechanism of action, as well as their potential to increase the cell killing effect of radiation. In the past, the selection of drugs for this concomitant use has mostly been based on *in vitro* and *in vivo* screening studies. In the future, however, this selection procedure should be focused on (1) the mechanism of action of candidate drugs and their capacity to influence pathways leading to cell death after irradiation, and (2) knowledge of the characteristics of individual tumours, such as the growth rate, and sensitivity to drugs and to radiation. New assays, especially micro-arrays, and the refinement of more conventional diagnostic tests provide us with much more knowledge of the tumour and its expected response to therapy. This research will allow the selec-

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tion of the most suitable treatment for each individual patient. Insight into the amplification of genes and proteins related to response to treatment provided by these assays may guide us towards the application of new treatment schedules and the introduction of new drugs in cancer treatment. The avoidance of exposing patients to ineffective and unnecessary treatments and their associated toxicity will also be a positive spin-off from such predictive assays.

This paper is meant to introduce combined modality treatment by highlighting the use of cisplatin and its potential for further exploration of its role in combined modality treatment. Many more attractive novel chemotherapeutic agents and biological response modifiers are now becoming available which are known to influence the cell-killing effect after irradiation. They offer the possibility to improve the efficacy of the concomitant use of radiotherapy and chemotherapy.

2. Rationale of combining radiotherapy and chemotherapy

The combination of radiotherapy and chemotherapy is mostly advocated because of its independent cell-killing effect. Radiotherapy is aimed at controlling the primary tumour, while chemotherapy is used to eradicate distant metastases. It is often argued that chemotherapy should also be used to reduce cell burden in tumours undergoing radiotherapy to obtain a higher local cure rate. However, this concept has failed in most clinical trials, probably due to fast repopulation of tumour cells after cytoreduction with chemotherapy before the start of radiotherapy [8]. A more attractive concept is the exploitation of the ability of chemotherapeutic agents to sensitise radio-resistant tumours to the lethal effect of ionising irradiation. *In vivo* and *in vitro* experiments showed an additive effect on tumour cell kill by combining radiotherapy with existing chemotherapeutic agents like cisplatin [9], mitomycin-C [10], and 5-fluorouracil [11]. Cisplatin has been selected from a large number of drugs as it demonstrated the largest enhancement in cell killing after irradiation. This research also showed that the timing between drug administration and irradiation significantly influenced the results. The largest therapeutic effect was seen when the drug was given daily before each fraction of the irradiation, although some limited increase of acute side-effects was observed in animals (Table 1).

A limitation of this approach is the risk of increasing the side-effects. Increased acute and late toxicity has been reported, for example, by the concomitant use of gemcitabine and radiotherapy [12]. Another restriction is the relative drug concentrations in the tumour are still low; this may also limit a successful clinical approach. Despite these limitations, a number of drugs (i.e. cisplatin, mitomycin-C, 5-fluorouracil) have demonstrated an improved clinical outcome after the concomitant use with radiotherapy. As discussed earlier, these results now form an important incentive for exploring and designing new drugs for the concomitant use with radiotherapy. Examples of promising preclinical results are combinations of irradiation with taxanes, nucleoside analogues (fludarabine, gemcitabine), topoisomerase 1 (topo1) inhibitors, etc. The mechanisms possibly responsible for the enhancement of the radioresponse include an increased induction of DNA double-strand breaks, inhibition of DNA repair after irradiation, cell-cycle redistribution, and induction of apoptosis.

3. Chemotherapeutic agents as radiosensitisers in clinical trials

Since the 1980s, many phase II trials have been reported with promising results in the treatment of squamous cell cancers of various origins with chemotherapy and radiotherapy given in a different sequence: before, during or after radiotherapy. It took, however, till the end of the last decade before convincing results of large randomised trials became available. These indicated that the concomitant administration of chemotherapy and radiation was consistently superior to radiation alone, not only in terms of local control but also in terms of improved survival [4,5].

In 1992, the Radiotherapy and Lung Cancer Cooperative Groups of the European Organization for Research and Treatment of Cancer (EORTC) reported the results of a randomised phase III study of concomitant cisplatin and radiotherapy versus radiotherapy alone in patients with non-metastatic inoperable non-small cell lung cancer. The results of this phase III trial indicated that the combination of cisplatin with radiotherapy was associated with improved rates of survival and control of local disease [2]. 331 patients (70% of whom had squamous cell cancer) were randomly assigned to one of three treatments: radiotherapy alone (group 1), the same radiotherapy combined with cisplatin at a dose of 30 mg/m^2 by intravenous (i.v.) infusion on the first day of each treatment week (group 2), or

Table 1
Dose-modifying factors (DMF) for concomitant radiotherapy and cisplatin

	Approximate DMF for cisplatin [Ref.]
Tumour	1.8–2.2 [9]
Skin	1.1 [9]
Small intestine	1.3 [9]
Rectum	1.1 [32]
Kidney	1.3 [33]
Lung	1.0 [34]

cisplatin at a dose of 6 mg/m^2 administered daily 1–2 h prior to radiotherapy (group 3). The largest and significant benefit was seen in the radiotherapy/daily cisplatin group. Both survival and control of local disease were significantly improved, compared with the radiotherapy-only group ($P=0.009$ and 0.003, respectively) (Fig. 1).

In April 1999, three articles in the *New England Journal of Medicine* reported on studies with chemo-radiotherapy versus conventional radiotherapy for locally advanced cervical cancer [3,13,14]. In all three studies, the combination of radiotherapy with cisplatin was significantly better than the control treatment arms, despite the fact that four different schedules for cisplatin were used in these three studies. An interesting observation came from Rose and colleagues [3], demonstrating that the single use of cisplatin was as effective as a combination of three drugs, the latter scheme being much more toxic. This group randomised 526 patients with locally advanced cervical cancer to receive either radiotherapy with cisplatin, 40 mg/m^2 weekly×6 (group 1), or radiotherapy with cisplatin, 50 mg/m^2, and 5-fluorouracil, 4000 mg/m^2/96-h at 4-week intervals×2, combined with hydroxyurea, 2000 mg/m^2 twice weekly for 6 weeks (group 2), or radiotherapy with only hydroxyurea, 3000 mg/m^2 twice weekly for 6 weeks (group 3). Progression-free survival and overall survival were significantly better for groups 1 and 2 than for group 3 ($P<0.004$), whereas no difference was found between the two cisplatin-containing regiments. The toxicity in the group that received multi-agent chemotherapy, however, was significantly worse than in the group receiving cisplatin alone.

In the meantime, three additional trials on the concomitant use of cisplatin in cervical cancer have been published, demonstrating now that five out of six trials had a significant improvement of local control and survival when concomitant cisplatin and irradiation was used (Table 2). This is in contrast with eight out of nine phase III studies of neo-adjuvant chemotherapy prior to radiotherapy in cervical cancer, showing no benefit, as reported in the literature (Fig. 2) [5].

A similar observation came from the recently published meta-analysis on the effects of chemotherapy in the treatment of locally advanced squamous cell carcinoma of the head and neck. Only chemotherapy given concurrently with radiotherapy provided significant benefits in terms of survival, whereas no significant benefit was associated with adjuvant or neo-adjuvant chemotherapy [4]. Recent trials in patients with head and neck cancer confirmed that the concomitant use of cisplatin or carboplatin and irradiation leads to improved local cure and survival when compared with radiotherapy alone [15]. Nevertheless, further improvement for advanced head and neck tumours is still needed considering the number of local recurrences.

In patients with anal cancer, it was shown in two randomised studies that concomitant radiotherapy and 5-fluorouracil and mitomycin-C significantly reduced the number of local recurrences (Fig. 3) [7,16]. Mitomycin-C has attributed significantly to these results as shown in a Radiation Therapy Oncology Group (RTOG) study [17]. In order to reduce the side-effects cisplatin has been used as a replacement for mitomycin-C, with good results in non-randomised studies [18]. Randomised studies are now underway to confirm at least equal efficacy of cisplatin and mitomycin-C. These anal cancer trials also clearly demonstrate the advantage of organ preservation by combined modality treatment as it results in the avoidance of colostomy in many patients (Fig. 4).

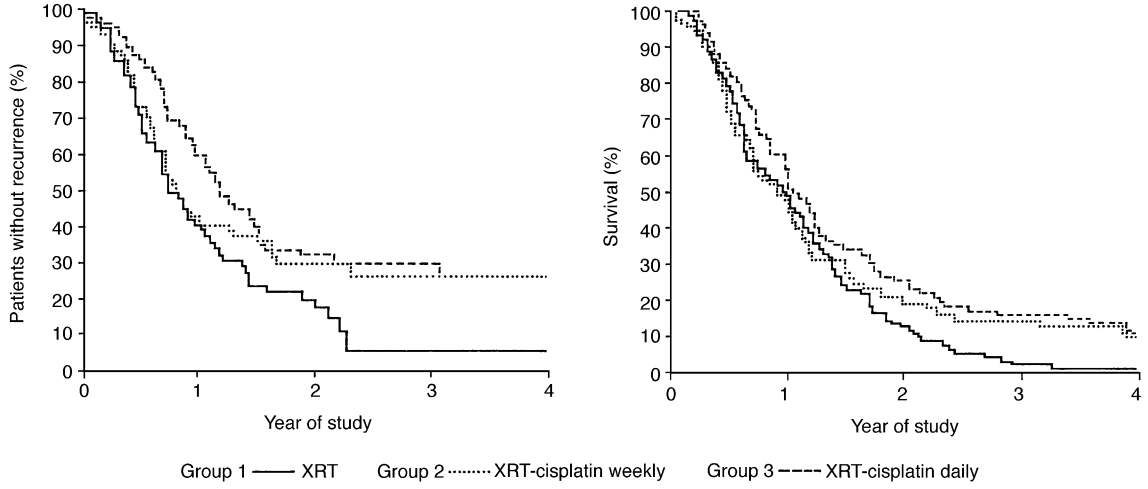

Fig. 1. Inoperable lung cancer: concomitant radiotherapy and cisplatin lead to improved local control and survival in lung cancer [2]. XRT, radiotherapy.

Table 2
Estimates of the relative risks (RR) of death in six clinical trials of concurrent chemotherapy and radiotherapy treatment for cervical cancer[a]

Reference	FIGO stage	Treatment		Relative risk of death in the comparison group
		Control group	Comparison group	
[14]	IB2	Radiotherapy	Radiotherapy plus weekly cisplatin	0.54
[3]	IIB-IVA	Radiotherapy plus hydroxyurea	Radiotherapy plus weekly cisplatin	0.61
			Radiotherapy plus cisplatin, 5-fluorouracil, and hydroxyurea	0.58
[13]	IB2-IVA	Extended field radiotherapy	Radiotherapy plus cisplatin, and 5-fluorouracil	0.52
[35]	IIB-IVA	Radiotherapy plus hydroxyurea	Radiotherapy plus cisplatin, and 5-fluorouracil	0.72
[36]	IB or IIA (selected post-operatively)	Radiotherapy	Radiotherapy plus cisplatin, and 5-fluorouracil	0.5
[37]	IB-IIB	Radiotherapy	Radiotherapy plus weekly cisplatin	0.9

FIGO, International Federation of Gynecology and Obstetrics.
[a] Modified from Ref. [5].

4. Ways to further improve the efficacy of concomitant radiotherapy and chemotherapy

A possible limitation of the combination of cisplatin and irradiation is the relatively low concentration of cisplatin in human tumours when the drug is given intravenously. New approaches resulting in a higher tumour concentration of this drug should therefore be explored. This is based on the observation in preclinical models that higher doses of cisplatin in combination with irradiation result in increased tumour cell death [9]. One of the possibilities is intra-arterial cisplatin given weekly concomitant to irradiation, with five doses of 150 mg/m^2 with i.v. Na-thio sulphate rescue [19]. Whether the chemotherapy should be given selectively by intra-arterial infusion, or i.v. is currently under investigation in a multi-institution study in The Netherlands.

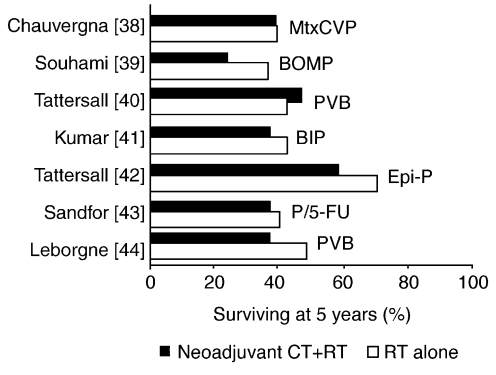

Fig. 2. Carcinoma of the cervix: neo-adjuvant trials did not show improvement in survival despite the large number of partial and complete remissions. Moreover, in some trials survival following neo-adjuvant chemotherapy was worse than for patients receiving radiotherapy alone. CT, chemotherapy; RT, radiotherapy; 5-FU, 5-fluorouracil. Modified from *Radiat Res* 2000, **154**, 229–236 [45].

Another approach to increase the efficacy of this combined treatment is the addition of drugs that may further improve the efficiency of the combination, such as hypoxic cell killing agents (tirapazamine) [20], or topoisomerase 1 (topo1) inhibitors [21]. A third possibility is to introduce a method of selection in the clinic to determine which tumours are sensitive to cisplatin. In all likelihood, a positive effect of the combined use of cisplatin and radiotherapy will only occur in patients with tumours sensitive to cisplatin [22]. One can conclude that the measurement of the drug concentration and sensitivity to cisplatin should be performed, so that the full course of cisplatin and radiation can be given to patients with cisplatin-sensitive tumours. Measurement of cisplatin sensitivity and drug concentration in human tumours has become possible by the development of antibodies against cisplatin DNA adducts [23]. In a group of lung cancer patients, it was shown that those with a high concentration of cisplatin DNA adducts in

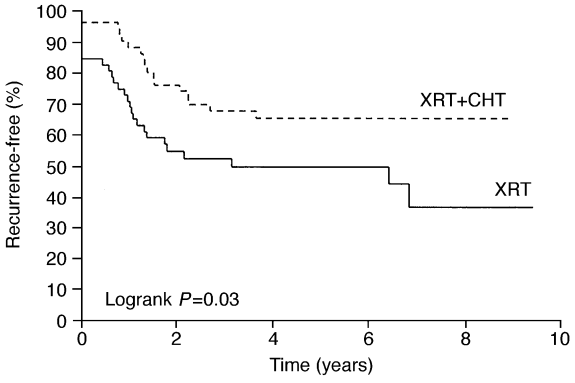

Fig. 3. Locally advanced anal cancer. Improvement of local control by adding concomitant, 5-fluorouracil and mitomycin-C [7]. XRT, radiotherapy; CHT, chemotherapy.

the buccal mucosa had a significantly better prognosis than those with low concentrations (Fig. 5) [24]. To optimise the benefit of concomitant radiotherapy, the combination should preferably be used only in patients shown to have a high tumour drug uptake or when the tumour is sensitive to cisplatin.

5. New opportunities for concomitant radiotherapy and chemotherapy

In this issue, several new possibilities for the combination radiotherapy and systemic treatment are discussed, varying from combinations of radiotherapy with classical cytostatic drugs, to promising new agents recently introduced in the clinic. Exciting is the search for new molecular targets for chemo–radiotherapy interactions, as one can predict increased efficiency and reduced side-effects of this combination due to the selectivity of the drugs.

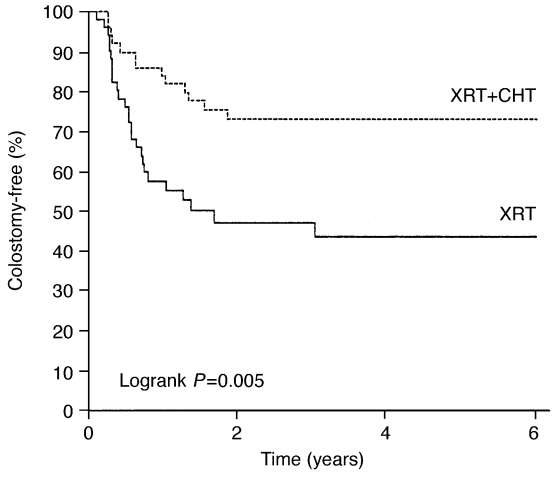

Fig. 4. Time to colostomy: the colostomy-free rate was improved by concomitant 5-fluorouracil and mitomycin-C and radiotherapy in advanced anal cancer. XRT, radiotherapy; CHT, chemotherapy.

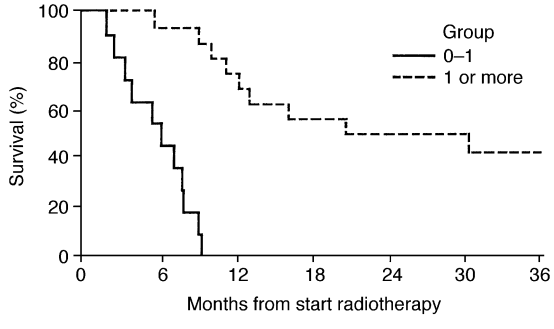

Fig. 5. Predictive potential of cisplatin adducts in buccal cells. Curves show survival of non-small cell lung cancer (NSCLC) patients given daily combined treatment with concomitant cisplatin and radiotherapy. Patients were grouped according to whether adduct levels were above or below the median value of 1.16. Adducts associated with increased radioresistance were quantified immunocytochemically on an arbitrary scale [24].

There are also other promising alternative drug–radiotherapy combinations in addition to cisplatin, for example employing the topo1 inhibitors topotecan and irinotecan. Topo1 inhibitors are novel and safe anticancer agents, which have become standard treatment in advanced ovarian and colorectal cancers. The sole target is the topo1 enzyme and they act by stabilising the topo1/DNA cleavable complex (cc). The combination of radiation and a topo1 inhibitor showed a strong synergistic cytotoxicity *in vitro* in the sequence radiation first followed by the topo1 inhibitor (data not shown). The number of cc were significantly increased by this combination. This seems to confirm the sequence-dependent synergistic cytotoxicity of a topo1 inhibitor and cisplatin that was recently described. Van Waardenburg and colleagues, showed a direct interaction between topo1 protein and platinum DNA adducts, which hinders the topo1 activity by interfering with the religation step and which results in a significant increase in topo1 cc formation. In patients, cisplatin and topotecan or irinotecan can be combined.

The use of novel molecular biological response modifiers in clinical studies may further improve radiotherapeutic results. We have generated evidence that synthetic membrane-permeable alkyl-lysophospholipids (ALPs) exert a potent and preferential cytotoxic effect on malignant cells, strongly enhance the radiation-induced cell kill and interfere with angiogenesis *in vitro* [25]. Unlike most currently available cytostatic drugs, ALPs target the plasma membrane and interfere with normal phospholipid metabolism and mitogenic signal transduction pathways. These biological properties, combined with our clinical experience on the toxicological and pharmacological profile of ALPs, make these compounds attractive model substrates to be combined with radiotherapy in patients. A phase I clinical study combining oral ALP and radiotherapy in patients with advanced solid tumours has recently been initiated at our institute.

Another strategy that has been pursued to enhance the radiation response involves blockade of growth factor receptors, including the epidermal growth factor receptor (EGFR), a member of the ErbB receptor tyrosine kinase family. Overexpression of the EGFR has been correlated with increased radioresistance, more aggressive behaviour, and poor clinical outcome [26]. Conversely, blockade of the EGFR by the monoclonal antibody C225 (Cetuximab) increased the *in vitro* radiosensitivity of various squamous cell carcinoma cell lines [27]. Additional preclinical data confirming these studies were generated in nude mice bearing A431 squamous cell carcinoma xenografts [28]. A more than 3-fold increase in tumour response after irradiation was observed when these animals received concurrent systemic C225. Possible cellular mechanisms, by which C225 enhances the response to radiation, include (1)

inhibition of proliferation, (2) induction of cell-cycle arrest, (3) enhancement of radiation-induced apoptosis, (4) inhibition of radiation-induced DNA damage repair, and (5) inhibition of angiogenesis [29]. Based on these preclinical studies, several clinical phase I/II trials have been successfully completed. Currently, a multicentre phase III trial is being conducted, randomising between radiotherapy with concomitant C225 and radiotherapy alone. Preliminary data indicate a high response rate in advanced head and neck squamous cell carcinoma with only mild, non-overlapping side-effects [30].

Mutated oncogenes offer an alternative approach for molecular targeting and radiosensitisation. An example of this is *ras* which is mutated in 30% of human tumours. These mutations are associated with increased radioresistance. For functional activity, the *ras* protein requires post-translational prenylation. Inhibitors of this process, e.g. farnesyl transferase inhibitors (FTI) can reverse the transformation and cause increased radiosensitivity. Some inhibition of tumour growth also occurs which is independent in tumours that do not harbour a mutated *ras* gene and that do not overexpress the *ras* protein [31]. FTIs in combination with radiotherapy have recently entered clinical trial for head and neck cancer.

6. Conclusion

Concomitant radiotherapy and chemotherapy has resulted in a major step forward in the treatment of patients with advanced solid tumours. The EORTC lung cancer study has provided strong evidence that the schedule of cisplatin administration may be critical, favouring daily administration of low doses of the drug, which is in line with animal experiments [2,9]. The schedule of once-daily low-dose cisplatin concurrently with radiotherapy is also both convenient and generally well tolerated. In this respect, measurement of cisplatin sensitivity and intratumoral drug concentration may be helpful to identify patients who would benefit from this combined modality treatment. The head and neck cancer and the cervical cancer trials also suggest that cisplatin is effective in improving the results when given concomitantly with irradiation. Further improvement is sought in increasing the cisplatin dose and in interaction with other drugs like hypoxic cell killing agents and topo1 inhibitors. In the coming decade, a number of new drugs will become available for testing in concomitant chemotherapy and radiotherapy approaches. These drugs should be selected based upon their mechanisms of action. Given the results of many randomised clinical studies, it is quite likely that chemoradiotherapy will be the standard of care for advanced squamous cell cancers, but until the best regimen of each disease has been determined, there is now more than ever an urgent need to encourage treatment of patients within the framework of carefully controlled clinical trials.

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