Clinical Oncology (2007) **19:** 397–417
doi:10.1016/j.clon.2007.03.010

Overview

Chemical Radiosensitizers for Use in Radiotherapy☆

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ABSTRACT:
Radiosensitizers are intended to enhance tumour cell killing while having much less effect on normal tissues. Some drugs target different physiological characteristics of the tumour, particularly hypoxia associated with radioresistance. Oxygen is the definitive hypoxic cell radiosensitizer, the large differential radiosensitivity of oxic vs hypoxic cells being an attractive factor. The combination of nicotinamide to reduce acute hypoxia with normobaric carbogen breathing is showing clinical promise. 'Electron-affinic' chemicals that react with DNA free radicals have the potential for universal activity to combat hypoxia-associated radioresistance; a nitroimidazole, nimorazole, is clinically effective at tolerable doses. Hypoxia-specific cytotoxins, such as tirapazamine, are valuable adjuncts to radiotherapy. Nitric oxide is a potent hypoxic cell radiosensitizer; variations in endogenous levels might have prognostic significance, and routes to deliver nitric oxide specifically to tumours are being developed. In principle, many drugs can be delivered selectively to hypoxic tumours using either reductase enzymes or radiation-produced free radicals to activate drug release from electron-affinic prodrugs. A redox-active agent based on a gadolinium chelate is being evaluated clinically. Pyrimidines substituted with bromine or iodine are incorporated into DNA and enhance free radical damage; fluoropyrimidines act by different mechanisms. A wide variety of drugs that influence the nature or repair of DNA damage are being evaluated in conjunction with radiation; it is often difficult to define the mechanisms underlying chemoradiation regimens. Drugs being evaluated include topoisomerase inhibitors (e.g. camptothecin, topotecan), and the hypoxia-activated anthraquinone AQ4N; alkylating agents include temozolomide. Drugs involved in DNA repair pathways being investigated include the potent poly(ADP ribose)polymerase inhibitor, AG14361. Proteins involved in cell signalling, such as the Ras family, are attractive targets linked to radioresistance, as are epidermal growth factor receptors and linked kinases (drugs including vandetanib [ZD6474], cetuximab and gefitinib), and cyclo-oxygenase-2 (celecoxib). The suppression of radioprotective thiols seems to offer more potential with alkylating agents than with radiotherapy, although it remains a strategy worthy of exploration. Wardman, P. (2007). *Clinical Oncology* 19, 397–417

Key words: Chemoradiation, DNA, hypoxia, nitroimidazoles, oxygen, radiosensitizers

Introduction

In the present context, the measures of radiosensitivity of most interest are the clonogenic survival of tumour cells, and the survival of cells in, or functionality of, normal tissues, after doses of radiation delivered with therapeutic intent. Variations in these measures of radiosensitivity reflect many factors. Differences in response with radiation quality might arise from different distributions of the initial ionization events, leading to differences in the nature, yields and/or spatial distribution (especially clustering) of damage from the free radicals that are the ultimate cause of cell death or pathological change. Chemicals — oxygen is an example — can react with these free radicals and modify response. Differences in radiosensitivity might reflect variations in the levels or activity of proteins involved in the repair of damage to DNA, linked in turn to gene expression: chemicals that inactivate such proteins might be radiosensitizers. As cells progress (or not) through the cell cycle, checkpoints and signalling events may vary in their efficiencies, and can be modified by drugs.

We consider here only the modulation of radiosensitivity by low molecular weight chemicals. These can be both endogenous substances, such as oxygen, nitric oxide, thiols and ascorbate (the levels of all of which can both vary and be modulated), and xenobiotic chemicals, which interact with radiation damage in some way. They can be further separated into substances that react with short-lived free radicals and need to be present at the instant of irradiation (e.g. oxygen), and those that target radiation effects more indirectly, such as by binding to DNA repair enzymes or cell

☆ The chemical structures of many of the drugs referred to in this overview are shown in Fig. 1; these are asterisked on first mention.

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signalling proteins to render them ineffective. Radiation therapy is often given in conjunction with a course of chemotherapy; in some instances this includes regimens in which therapeutic gain is sought by exploiting synergy between radiation and drug effects. An example would be the combination of drugs that kill radioresistant hypoxic cells with a radiotherapy course. Although the planning of such a regimen would consider the two treatments in concert because the target cell population varies during the radiotherapy course because of differential radiosensitivity of hypoxic vs oxic cells, the effects are in principle independent, and this topic is not discussed here. However, some drugs may both kill hypoxic cells *and* react with short-lived, radiation-produced free radicals; these are discussed below. Furthermore, the independence of action is often a grey area: if one defines radiation effects to include a long post-irradiation period, it may be unclear whether any effects of chemotherapy given any time after irradiation are truly independent of radiobiological effects. The terminology in discussing the interaction of cytotoxic chemotherapy with radiation has long been a problem [1,2], yet 'our understanding of the specific mechanisms of interaction between radiation and chemotherapy is still evolving' [3]. The present overview cannot hope to encompass all aspects of the interaction of radiation with drugs; a recent review [4] set out the general principles of the 'concurrent chemoradiation paradigm', and previous papers have discussed the biological basis for combining drugs with radiation [3] and reviewed many trials of combined radiation/drug treatment [5]. A comprehensive overview of both radiation sensitizers and protectors showed the breadth of the topic [6]; new and emerging radiosensitizers and radioprotectors have been reviewed recently [7], focusing on the newer chemoradiation modalities. A report of a meeting to advise the International Atomic Energy Agency on radiosensitizers meriting further development also described the newer approaches [8].

Chemical radioprotectors are, of course, the reverse of radiosensitizers: the aim is to decrease radiosensitivity, especially of normal tissues. Clinical gain can be either by a reduction in morbidity if the effects are confined to normal tissues, or by exploiting the hoped-for reduced radiosensitivity of normal tissues to deliver higher radiation doses and, thus, enhanced tumour cell kill, the latter strategy obviously not without risk. The best-known radioprotector is the thiol prodrug, amifostine* (WR-2721). Activity in this field has been included in other reviews [6,7,9–12] and is not discussed in detail here. The importance of chemical radioprotectors is that their existence illustrates the competition between the enhancement of damage (e.g. by oxygen or drugs) and 'repair' in the specific example involving the reaction of short-lived free radicals with thiols, or thiol drugs [6,9].

As key discoveries in the 1970s relevant to this area are becoming less well known with time (an example is the millisecond timescale of the 'oxygen effect' [13,14]), some early landmark advances are noted, along with a brief overview of the current status. The field is too large for a comprehensive survey in this overview, and only illustrative references are given.

Types of Chemical Radiosensitizer

An early pioneer in this field, G. E. Adams, divided radiosensitizers into five categories [15,16]:

- 'Suppression of intracellular-SH [thiols] or other endogenous radioprotective substances.
- Radiation-induced formation of cytotoxic substances from the radiolysis of the sensitizer.
- Inhibitors of post-irradiation cellular repair processes.
- Sensitization by structural incorporation of thymine analogues into intracellular DNA.
- Oxygen-mimetic sensitizers, for example the electron-affinic drugs …'.

All these types of radiosensitizer are discussed below, although the order and emphasis is changed, and there is new interest in cell signalling processes and growth factors so that post-irradiation pathways of interest extend beyond DNA repair.

Another leader in this area, E. J. Hall, in discussing radiosensitizers, stressed the importance of a differential effect between tumours and normal tissue, and with this 'all important criterion' suggested in the fifth edition of his standard text [17] 'only two types of sensitizers have found practical use in clinical radiotherapy:

- The halogenated pyrimidines … based on the premise that tumor cells cycle faster and, therefore, incorporate more drug than the surrounding normal tissues.
- Hypoxic cell sensitizers increase the sensitivity of cells deficient in molecular oxygen … based on the premise that hypoxic cells occur only in tumors and not in normal tissues.'

This focus now seems too narrow to the present author, or at least 'hypoxic cell sensitizers' can now be broadened as a term far beyond the original concept. Taking up the latter premise presented by Hall (recognising that the issue is not clear-cut, with a spectrum of oxygen tensions across both tumours and normal tissues), it is pertinent to note recent progress in oxygen-sensitive drug delivery. In principle, many drugs can be specifically released only in cells of low, defined oxygen tension, exploiting the 'trigger-effector' concept, developed especially by the group of W. A. Denny and W. R. Wilson [18], and now attracting wider attention [19,20]. This approach, illustrated in Fig. 2, involves constructing prodrugs comprising a bioreducible 'trigger' (often nitroaromatic moieties based on experience with 'electron-affinic' radiosensitizers), which when reduced by cellular enzymes (donating an electron to form a radical anion), fragments to release active drug. This release can be made selective to hypoxia because the intermediate prodrug radical is oxygen reactive; oxygen inhibits drug release via a fast, free radical (electron transfer) reaction. Profiling drug release to oxygen tensions involves matching the rates (chemical kinetics) of the reactions involved [21]. A recent illustration from the author's institute shows significant