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ABSTRACT

This review describes some current and future approaches designed to modulate the response of tumors and normal tissues to cell killing by ionizing radiation. The emerging knowledge of tumor, cellular and molecular biology is providing a better understanding of the clinical results with the hypoxic cell sensitizers and novel approaches to radiation sensitization and protection. The Oncologist 1996;1:227-231

INTRODUCTION

This Symposium is dedicated to Dr. Bruce Chabner, the retiring Director of the Division of Cancer Treatment, and contains many presentations from the medical oncologists and pharmacologists trained by him. Dr. Chabner's contributions to drug development have also extended to the field of radiation oncology. As Bruce's second Clinical Associate, I have had the opportunity to use medical oncology, pharmacology and biochemistry training from the Medicine Branch and Laboratory of Chemical Pharmacology to help with the preclinical and clinical development of radiation sensitizers and enhancers.

The concept of altering the radiation sensitivity has been known for approximately 60 years, since the discovery of the relative radioresistance due to hypoxia. This paper will use the development of antihypoxic modifiers as a model for the progress in drug development and will then present some of the opportunities currently available for radiation sensitization and protection. Only a few salient citations will be included, with more complete reviews listed in the references [1-4].

APPROACHES TOWARD HYPOXIA

Historical Perspective

In an attempt to enhance the efficacy of clinical radiation therapy, hypoxic cells were a major target because it takes approximately three times the radiation dose to achieve the same proportion of cell survival under hypoxia compared to cells in normoxic conditions. The biochemical role of oxygen was in fixing, or making permanent, the damage done to the critical DNA target. Radiation can damage DNA either by direct interaction or indirectly by the ionization created in nearby water molecules [5]. The Competition Model of DNA damage was proposed many years ago [2] and described a competition between oxygen for damage fixation and reducing species, such as thiol compounds (-SH), for chemical restitution.

The earliest approach was the use of high pressure oxygen. This required the patient to be treated in a hyperbaric chamber which is a technical tour de force. Due to the complexity of the procedure, only a limited number of hyperbaric treatments were administered. Normally, radiation therapy is given to patients in a course using many daily treatments. This is called fractionation and uses a daily dose of about 1.8-2.0 Gy to a total dose of approximately 50-70 Gy. When large daily doses are given, the risk of late normal tissue damage increases [5]. Also, it has been demonstrated in murine systems that reoxygenation occurs after each radiation treatment. Reoxygenation is the process by which the proportion of hypoxic cells returns to baseline a few hours after each radiation treatment rather than gradually increasing, which would occur when the well-oxygenated cells are killed. Due to the technical complexity in treatment delivery, most of the hyperbaric oxygen trials used few large doses of irradiation, which had the deleterious effects of increasing normal tissue injury and eliminating the potential benefits of reoxygenation due to insufficient fractionation. The majority of the hyperbaric oxygen trials were null in that there were no benefits [6]. Currently, the use of normal pressure or hyperbaric oxygen is being explored using oxygen carriers such as the perfluorochemicals [7] or carbogen with agents that alter tumor blood flow, such as nicotinamide [8] (e.g., the ARCON regimen of accelerated radiotherapy, carbogen and nicotinamide).

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The earliest clinical trials with hypoxic cell radiosensitizers were based on the 5- and 2-nitroimidazole compounds [1, 2, 9]. A classic randomized trial using the 5-nitromidazole metronidazole [9] for patients with brain tumors was positive in that the survival of the sensitizer arm was better than that of the control. However, in this trial a nonstandard radiation fractionation scheme was utilized (i.e., fewer large-sized fractions) and it turned out that the metronidazole arm fared no better than the historical controls who had been given standard fractionated irradiation. This was encouraging for the concept of chemical modifiers because this trial displayed clinical activity to sensitizers, but also emphasized the need to have a sensitizer that could be used with many radiation fractions in a course of standard radiotherapy.

The next drugs tested were misonidazole and its metabolite desmethylmisonidazole. These agents produced a dose-limiting neurotoxicity such that only six relatively high doses of drug could be administered or a very reduced dose could be given with multiple fractions. Overall, the clinical trials with these agents were null [1, 2].

The next 2-nitroimidazole agent to be studied, etanidazole, was developed based on the pharmacokinetic principle that a less lipophilic analog of misonidazole would both be less neurotoxic and more rapidly excreted so that drug exposure as measured by the area under the concentration versus time curve (AUC) would be reduced. As predicted, this agent was about one-third less toxic than misonidazole so that approximately 18 doses could be administered [10].

Current Status of Hypoxic Sensitizers

While hypoxia has been targeted for a number of years, only recently has hypoxia been demonstrated in human tumors [1, 2, 10]. Pretreatment measurements of tumor oxygen content prior to irradiation in patients with breast, head and neck, and cervix cancers have demonstrated the presence of radiobiologic hypoxia in about half of the tumors. No normal tissues had hypoxic cells so that antihypoxia therapies should be relatively tumor-specific. The natural history of oxygenation status during a course of radiation therapy for tumors that start out either hypoxic or normoxic remains to be determined. This is very important since the ability to select patients for radiation sensitizer trials based on their tumor hypoxia would provide a population of patients most likely to benefit from an antihypoxic treatment. Both biopsy- and imaging-based hypoxia measurement techniques are being developed [11].

Recent randomized clinical trials of hypoxic cell sensitizers have given conflicting results. Overgaard has reported a positive trial using the 5-nitroimidazole, nimorazole, with each fraction for patients with pharyngeal cancer [1, 2]. On the other hand, a randomized Radiation Therapy Oncology Group (RTOG) head and neck trial demonstrated no benefit to the use of etanidazole with 17 fractions of a 30-35 fraction regimen. Subset analysis suggested a benefit to patients with smaller lymph nodes (N_0-1 compared to N_2-3), however, subset analyses are only valid for hypothesis generation and not for proof of principle.

When a large single dose of radiation is administered, hypoxic cells are more likely to be a problem. For this reason, etanidazole is to be evaluated by the RTOG for patients receiving stereotactic radiosurgery or intraoperative radiotherapy, both of which use a single dose of about 15-18 Gy. At this point in time, the future clinical role for the hypoxic cell radiosensitizers is uncertain [10, 12].

Hypoxic Cytotoxic Agents

The drug development effort designed to produce superior hypoxic cell radiosensitizers led to a new class of compounds called radiation enhancers or bioreductive agents. These agents directly kill the hypoxic cell with a much smaller amount of cell killing of oxygenated cells. Unlike the hypoxic sensitizers which must be present at the time of irradiation, these agents can be effective if given either shortly before or after irradiation [13]. One agent under clinical investigation is tirapazamine (SR-4233) which has muscle cramping as its major clinical toxicity. Tirapazamine can also enhance the efficacy of chemotherapeutic agents such as cisplatin. Other classes of bioreductive compounds, the mitomycin C analog E09 and the 2-nitroimidazole CI-1010, are in preclinical and clinical development. The reductive enzymes needed for drug activation and inactivation will vary with the specific drug. Therefore, in the future it may be possible to target bioreductive drugs specifically to an individual patient’s tumor based on the enzymatic profile [14].

Modulating the Modulators

The tripeptide glutathione can potentially interfere with the efficacy of the hypoxic sensitizers and hypoxic cytotoxic agents [1, 2]. It is possible in the clinic to deplete intracellular glutathione with an agent L-buthionine sulfoximine and thereby increase the efficacy of the antihypoxia drugs. Thiol-based compounds such as WR-2721 (amifostine) have been developed as potential radio- and chemoprotectors [2]. Thus, thiol manipulation provides a potential for therapeutic gain.

Another way of increasing the efficacy of the currently available agents may be through an understanding of their normal tissue toxicity: the neurotoxicity of etanidazole [1, 2, 15] or the aerobic cytotoxicity of tirapazamine [16]. With the knowledge of the mechanism of normal tissue toxicity, it may be possible to increase the effectiveness of the antihypoxia agent by selectively ameliorating their aerobic effects.
Nonheritable Resistance

The tumor microenvironment is characterized by nutrient deprivation. The models proposed in the past were based on the presence of a static depletion such as chronic hypoxia. However, a number of years ago, intermittent hypoxia was demonstrated in murine tumors [1, 2]. Intermittent perfusion means that a cell may be normoxic at one point in time and hypoxic just a few minutes later. When the hypoxic fraction of a tumor is determined, it is based on measurements which provide the percentage of hypoxic cells at the time of assessment. However, with intermittent hypoxia, it is possible that a far greater percentage of cells are hypoxic at some time compared to the instantaneous hypoxic fraction. This might not only expose more cells to hypoxia, but the process of hypoxia-reperfusion may be a source of oxidative stress.

A number of studies reported that hypoxia can induce transient phenotypes important in cancer progression and therapeutic resistance such as drug resistance, increased metastatic potential, cell cycle delay and the induction of growth-arrest genes [1, 2]. Hlatky has recently demonstrated that tumor hypoxia can induce the angiogenic factor VEGF (vascular endothelial growth factor) in breast cancer fibroblasts [17]. The induction of VEGF in the fibroblasts was greater than that seen in the tumor cells. Thus, critical molecules involved in treatment resistance or tumor progression may be inducible by the microenvironment and add to the phenotypic diversity and heterogeneity of the cancer cell. The elucidation of these epigenetic processes and their mechanism will provide a much greater understanding of the in vivo resistance seen in murine systems and the clinic [18].

Radiation Biology, 1995

Figure 1 is a schematic of the various processes involved in modern radiation biology. Each of these processes is complex in its own right, however, this diagram indicates the wide range of potential new therapies.

Starting in the nucleus, the primary target of radiation damage is the DNA. Paralleling the hypoxia story has been an interest in understanding DNA repair, as it was thought that this might be a major target for radiation modifiers. Indeed, agents that alter DNA damage and repair, such as the halopyrimidines, are in clinical trials [3]. In addition to repair, the importance of recombination has recently been recognized [19].
Radiation is known to induce cell cycle changes, and the molecular mechanisms are being elucidated [20]. Apoptosis can occur after ionizing radiation [21]. Whether apoptosis, independent of clonogenic death, is important in clinical radiation therapy remains to be elucidated. However, apoptosis may provide a unique target of enhancing the radiation response.

It is not yet known how the cell senses radiation. A number of signal transduction pathways are activated [22, 23], but the relative importance of each in the response of the cell and cell survival remains to be seen. Protein kinase inhibitors are now being explored as novel radiation modifiers, and many new inhibitors are being developed [24]. Following radiation, a series of radiation-induced proteins are observed that are being elucidated by Boothman [25]. Similarly, the gadd genes are inducible by both ionizing irradiation [26] and hypoxia [27]. The genetic mutations, such as p53, that are involved in tumor progression may also be involved in cell survival following irradiation [28].

The growth factor milieu can determine the cellular response to irradiation. For example, bFGF can serve as a radioprotector for endothelial cells [29]. Additionally, cytokines can be secreted at varying times after radiotherapy. One such cytokine, transforming growth factor β [30, 31] has been implicated in radiation injury. In the future, it might be possible to use agents that alter the progression of chronic radiation injury after the course of irradiation, thereby avoiding possible tumor radioprotection.

There are a number of possible approaches using gene therapy with radiation therapy. These range from using radiation-responsive elements [32], genes and prodrugs that produce a high local concentration of a radiation modifier [33, 34] and genes that alter the cellular composition within the tumor [35]. Such approaches take advantage of the targeting of the radiation therapy and not just the targeting of the gene. Clearly, much remains to be done toward making a sufficiently specific gene-toxin construct.

**SUMMARY**

Although radiation therapy is a physical modality, there are many possible mechanisms by which to alter the cellular response to ionizing radiation. These involve drug development which requires the use of pharmacological, biochemical and molecular biologic principles. The field of radiation oncology has greatly benefited from the drug development program supported by the Division of Cancer Treatment and the clinical trials under the auspices of the Clinical Trials Evaluation Program and RTOG. Dr. Chabner has been a very strong scientific and administrative supporter of these radiation modifier trials which have led to new clinical agents and novel biological concepts.

**EPILOGUE**

Dr. Chabner’s contributions to the research and careers of those fortunate enough to work with him extend well beyond the scientific content of the papers. Dr. Chabner and his wife Davi have served as role models and inspirations for so many. They have demonstrated true family values in how they care for their family and raised their children. Their kindness and generosity extended to their many, many friends. The Chabners are people of enormous honesty, integrity, humility and humanity.

Scientific fact changes daily but outstanding character and personal traits such as these endure and are of timeless value. I am fortunate to be among the group of clinical associates who have been trained by Bruce and influenced by him. I am particularly fortunate to be unique among his trainees to welcome him as a colleague in his move to Harvard Medical School. The oncology community in Boston looks forward to the infusion of his ideas into our research and training programs. As he has done in some of the more trying moments at the National Institutes of Health, Bruce will serve as a beacon of fairness and reason in the murky seas of health care reform and shrinking research dollars. Continuing on the path he started early in his career, he will remain a conscience for academia, serving as a constant reminder of the real reasons we engage in careers in oncology—to bring better treatments and cures to patients with cancer.

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