Do Radiosensitizers Enhance the Treatment of Patients With NSCLC?*

The Need for Better Models and Alternative Methods of Treatment

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Radiotherapy as a treatment for non-small cell lung cancer (NSCLC) can potentially be optimized by the use of radiosensitizers, substances that enhance the effect of radiation on tumor tissue without an equal increase in the effect on normal tissue. Radiosensitizers may act by increasing the level of lethal damage caused by radiation or by causing a decrease in the repair of such lethal damage. While cell and animal models have been used in an attempt to establish the efficacy of radiosensitizers, trials in man have so far been inconclusive. The need to improve existing models and methods for combining modalities to best effect is clear. Radiotherapy/chemotherapy combinations are a logical alternative to radiosensitizers for managing NSCLC, and despite variability in the extent of local and metastatic control, evidence for improved survival exists.

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Where radiotherapy is used in the treatment of non-small cell lung cancer (NSCLC), the option to enhance this treatment by the use of radiosensitizers arises. Radiosensitizers act to enhance the effect of radiotherapy in the treatment of tumors without equally increasing the effect of radiation on normal tissues. While a true radiosensitizer has no effect on either tumor or normal cells when used alone, its use in conjunction with radiotherapy produces synergistic responses, the combined effect being greater than the sum of the two. Radiosensitization may increase the amount of lethal damage arising from irradiation of tumors or may decrease the ability of tumors to repair such damage.

Current possibilities for increasing the lethal damage by irradiation are based on decreasing the number of hypoxic cells. For about 60 years, it has been known that the effect of irradiation is more pronounced in tumor areas in the neighborhood of blood vessels. Several methods in current use try to increase oxygenation of tumor cells, a good example being that of carbogen (a mixture of 95% oxygen and 5% carbon dioxide). Nicotinamide, the amide derivative of niacin (vitamin B₃), improves the oxygenation of tumors by increasing the uniformity of blood perfusion. Combination of both (carbogen and nicotinamide) gives an enhancement ratio of irradiation of about 1.83, at least in experimental models. Reducing the intracellular thiol concentration by administering drugs such as misonidazol, buthionine-sulfoximine, and diethyl malate can decrease the ability of radical scavenging, resulting in a higher chance of fixation of damage and a decrease of repair mechanisms. These drugs are often highly toxic, however, and in general, have not been routinely tested. A third possible strategy for radiosensitization is to modify DNA using bromodeoxyuridine. This drug replaces thymidine in the DNA chain and makes it more sensitive to radiation damage because normal repair mechanisms cannot be used any more.

Radiosensitization as an aid to radiotherapy is distinct from radioprotection, where normal tissue is protected from the radiation treatment so that higher doses can be administered to enhance tumor cell kill. Drugs such as cysteamine (β-mercaptopo-ethylamine) and amifostine (WR-2721) protect normal tissues by radical scavenging, eliminating free radicals preferentially from the normal tissues. Again, toxic reactions can be problematic, for example hypotension with amifostine in doses above 1,100 mg/m². Amifostine is clinically useful because this protective agent is rapidly absorbed by normal tissues and slowly by tumor tissues. Due to this difference, normal tissues will be protected from radiotherapeutic or chemotherapeutic aggression.

**Proving Radiosensitization**

**Cell Models**

Radiosensitization has been demonstrated at the cellular level, using different types of cells in culture. In these classic models, survival is plotted against radiation dose. If radiosensitization is successful, there is
Table 1—Advantages and Disadvantages of Combining Radiotherapy With Chemotherapy*

<table>
<thead>
<tr>
<th>Modality</th>
<th>Potential Benefit</th>
<th>Potential Drawback</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy first</td>
<td>Vascular access</td>
<td>Delayed radiotherapy, initial drug resistance, earlier systemic toxic reaction</td>
</tr>
<tr>
<td>Radiotherapy first</td>
<td>Local efficacy</td>
<td>Growth of micrometastases</td>
</tr>
<tr>
<td>Concurrent</td>
<td>Cumulative action, radiosensitization, cellular interaction</td>
<td>Cumulative action, cumbersome</td>
</tr>
<tr>
<td>Sandwich</td>
<td>Lower toxic reaction</td>
<td>Lower efficacy, tumor regrowth</td>
</tr>
</tbody>
</table>

*Modified from Raghaven.3

a clear shift of data to the left of the graph. If regrowth delay is plotted against radiation dose, there is a shift of the curve to the right. In cell models, the enhancement ratio is typically between 1.1 and 2.1.1 However, the value of cellular studies is limited and clinically unrealistic, as only a single dose of radiation is given. In these models, there is no problem of heterogeneity of the tumor cells and there is no influence of possible hypoxia.

Animal Models

In animal models, fractionated doses of radiation can be administered, which mimics common clinical situations. Hyperfractionation is also feasible and has shown to be sparing of normal tissue; tumor proliferation is prevented during therapy. In animal models, radiosensitivity due to several drugs and techniques has been proved.

Enhancement ratios of 1.2-2.1 for the combination of carbogen-nicotinamide has been demonstrated in implanted tumors in mice.2 These studies have their limitations, as animal toxic reactions are seldom predictive of human toxic reactions, as well for acute, late, or cumulative toxic reactions. Again, animal tumors or even xenografts of human tumors in rodents are not realistic models, but just indicative for screening.

Human Models

In human models, proof of radiosensitization has not been conclusive after several decades of research. Radiosensitization is currently being explored as part of the ongoing European Organization for Research and Treatment of Cancer accelerated radiotherapy with carbogen and nicotinamide (ARCON) phase I and II trials in the treatment of NSCLC, head and neck cancer, and bladder cancer. The ARCON trial combines accelerated radiotherapy with the administration of carbogen and nicotinamide as radiosensitizers. Accrual is proving difficult, particularly in lung cancer patients who experience extreme distress in breathing almost pure oxygen minutes before radiotherapy. The daily hyperfractionation of radiotherapy causes additional early toxic reactions, raising questions about quality of life. The additional physician's time needed for treatment—which can be two to three times that of conventional radiotherapy—adds significantly to the cost. It is clear that the complexity of such a treatment has a negative impact on its feasibility.

Optimizing Clinical Models

General feelings on the feasibility of ARCON are that carbogen is more promising than nicotinamide, but as accelerated radiotherapy is not yet proved, combining these three treatment steps in one study may be leap too far at this stage. The main concern among researchers is finding a successful protocol. Problems encountered in clinical studies stem from toxic reactions and patient dissatisfaction, and there is a need to establish different models and improve methods.

Table 2—Combined Modality Trials of Chemoradiotherapy in Surgically Unresectable NSCLC*

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>Radiation Therapy</th>
<th>2-yr Survival, %</th>
<th>Median Duration of Survival, mo</th>
<th>Local Failure, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>FLSG</td>
<td>CAP</td>
<td>Split course, 55 Gy</td>
<td>19/17</td>
<td>311/332 d</td>
</tr>
<tr>
<td>SWOG</td>
<td>FOMI/CAP</td>
<td>55 Gy</td>
<td>—</td>
<td>9.1/9.2 mo</td>
</tr>
<tr>
<td>CALGB</td>
<td>VP</td>
<td>60 Gy</td>
<td>26/13</td>
<td>13.8/9.7 mo</td>
</tr>
<tr>
<td>NCCTG</td>
<td>MACC</td>
<td>60 Gy</td>
<td>21/16</td>
<td>19/192 d</td>
</tr>
<tr>
<td>le Chevalier</td>
<td>VCPC</td>
<td>65 Gy</td>
<td>21/14</td>
<td>12/10 mo</td>
</tr>
<tr>
<td>Schaalke-Koning</td>
<td>VP</td>
<td>Split course, 55 Gy</td>
<td>26/13</td>
<td>—</td>
</tr>
<tr>
<td>Trovo et al</td>
<td>every week</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Adapted from Sause.4

CALGB=Cancer and Leukemia Group B; CAP=cyclophosphamide/doxorubicin/cisplatin; FLSG=Finnish Lung Cancer Study Group; FOMI=5-fluorouracil/vincristine/mitomycin; MACC= methotrexate/doxorubicin/cyclophosphamide/5-fluorouracil; SWOG=Southwest Oncology Group; VCPC=vindesine/lomustine/cisplatin/cyclophosphamide; VP=vinblastine/cisplatin. NCCTG=North Central Cancer Treatment Group.

1Combination data/radiotherapy alone data.
The ideal model for testing radiosensitization for NSCLC treatment in man would be a randomized phase III trial of radiosensitizing therapy vs radiation alone, or radiosensitizing therapy vs radiotherapy combined with cisplatin. End points should be local control and improved survival. In addition, there is a clear need to examine the effects of combining radiosensitization with other drugs, such as the radioprotector amifostine. Ideal patients should have stage III disease, but this group is very “popular” for studies at this moment.

**Combining Radiotherapy With Chemotherapy**

A combination of systemic chemotherapy with locoregional radiotherapy, in which best local treatment is combined with best systemic treatment, is a logical alternative to radiotherapy alone or combined with radiosensitizers. However, this is not simple to achieve, as there are no optimal local or systemic chemotherapies or radiation schedules. There is, for example, 70% local recurrence of tumor growth after 60 Gy of locoregional therapy.

There is a dose-response relationship between radiation levels and tumor cell death, but a narrow margin exists between efficacy and complications. Optimal systemic treatment is lacking because of intrinsic or acquired resistance. Finally, combining the two treatment modalities provides its own difficulties in terms of increased and specific toxic reactions.

Goals in combining radiotherapy with chemotherapy include the enhancement of radiation damage to the tumor, the protection or sparing of normal tissue from damage during treatment, and the inhibition of tumor proliferation. These can be achieved by the spatial cooperation and independent toxicities of the two modes of treatment. Benefits and disadvantages of different schemes for combining radiotherapy with chemotherapy have been studied (Table 1). In all treatments, survival of “clinically local disease” is dependent on local tumor regrowth and clinically unapparent metastases.

Results of combined modality trials have been encouraging, showing some evidence of improved survival (Table 2). Data on local and metastatic control, however, have been mixed, with some studies showing good local control but no effect on distant metastasis and other studies showing the opposite effects. In general, the results of combined modality trials show an increased rate of survival over a 2-year period, though the median duration of survival was variable and sometimes lower in the combined therapy group. Cisplatin and cisplatin/vinblastine combinations with radiotherapy produced the most beneficial 2-year survival results compared with other chemoradiotherapy combinations or radiotherapy alone. Cisplatin combined with other chemotherapeutic agents, such as cyclophosphamide and doxorubicin, produced only a modest increase in 2-year survival rate and a lower median duration of survival compared with radiotherapy alone.

In a 5-year, three-armed randomized trial, Schaake-Koning et al attempted to assess acute and late toxic reactions and impact on survival of the combination of high-dose, split-course radiotherapy combined with cisplatin, 30 mg/m² weekly, or 6 mg/m² daily, compared with radiotherapy alone in patients with NSCLC. Long-term survival was improved and time to local progression was increased by combining radiotherapy plus cisplatin compared with radiotherapy alone (Fig 1 and 2).

Based on the results of these combined modality trials, it should be logical to start a study combining the most efficacious chemotherapy (to reduce distant metastasis) and the most optimal local treatment such as radiotherapy with daily cisplatin (to have best local...
control). It is not impossible that this optimal treatment—if it is feasible—can be improved by adding radioprotectors or radiosensitizers such as nicotinamide. It is clear that if radiotherapy was the cornerstone for locally unresectable NSCLC until now, it will not remain the “lonely standard” in the future.

References
1 Overgaard I. Importance of tumor hypoxia in radiotherapy: a meta-analysis of controlled clinical trials. Radiother Oncol 1992; 24:S64-8