

COMBINING CHEMOTHERAPY AND RADIATION

by: Gil Lederman, MD

Over recent years, many have attempted to combine chemotherapy with radiation for improved results of malignant tumors. Recent review of this topic by Ian Tannock in [The Journal of Clinical Oncology](#) reviews current data and potential benefits of this approach.

What is the rationale of combining chemotherapy and radiation? It may be that chemotherapy eradicates microscopic sites of disease that have yet to appear or manifest themselves. This certainly would be true if chemotherapy can indeed eradicate malignant cells. In this regard, interaction between the radiation and chemotherapy is not necessary.

Local tumor recurrence after radiation occurs if the radiation is not effective or the tumor cells are resistant to the effects of radiation. Using chemotherapy combined with radiation in this situation may be expected to improve local tumor outcome and therefore minimize cancer recurrence rates.

As Tannock points out, "The addition of a drug to radiation therapy will improve the therapeutic index only if cell killing in the tumor is increased more than toxicity to normal tissues. Alternatively, with adjustment of radiation dose, if necessary an improved therapeutic index requires that there be increased anti-tumor effects for equivalent toxic side effects."

Some drugs used to enhance radiation effects are called radiation sensitizers. These sensitizers mimic what oxygen does in the tumor cells, to increase the radiation damage and therefore improve outcome.

Drugs like Mitomycin are toxic to cells in low oxygen conditions - an interesting possibility to help eradicate tumors often present at less than optimal oxygen concentrations. Most oncologists believe that oxygen must be within a tumor for radiation to effectively kill cancers.

Radiation is given in fractions or intervals. Cells that survive these intervals and repopulate are called repopulated cells. Normal cells repair damage caused by radiation while repopulation of cancer cells is often manifested as resistance to treatment.

Exactly how drugs and radiation are given together is a subject of much study. Neo-adjuvant chemotherapy (or chemotherapy delivered before the curative surgery and/or radiation) is devised to shrink tumors before radical therapy. Its goal is to diminish the scope of surgery or radiation necessary.

Sites where combined modality therapy are commonly administered have been outlined. They include brain tumors where standard chemotherapy has shown "no or minimal benefit from the addition of chemotherapy." Tannock notes, "There may be a very small effective nitrosourea-based chemotherapy to improve survival when used with post-operative radiotherapy for gliomas, but it is debatable whether the level of benefit warrants the associated toxicity."

Head and neck cancers commonly in the mouth or throat areas has been the subject of intensive study using chemotherapy combined with radiation. Response rates are fairly high - up to 50%.

The author recommends, "At present, surgery and/or radiation should remain the standard treatment for squamous cell cancer of the head and neck. For locally advanced laryngeal cancer, either radiotherapy alone or chemotherapy (three courses of Cis-platin/Fluorouracil) followed by radiation may be selected for attempted laryngeal preservation, pending the results of an inner-

group trial comparing these approaches. Combined modality treatment with concurrent Cis-platin and radiotherapy with subsequent adjuvant Cis-platin and Fluorouracil may become standard for locally advanced nasopharynx cancer if early results of the inner-group study are confirmed with longer follow-up evaluation."

Review of treatment of non-small cell lung cancers, the most common type, reveals "a small but definitive role for radiation therapy has been established for treatment of Stage III non-small cell lung cancer." He notes improvement in survival using combined modality therapy. A large evaluation of more than 3000 patients shows an improvement in survival and a reduction in the annual risk of death.

Similarly for small cell cancer that is confined to the chest, a reduction in risk of death and improvement in survival was seen using combined modality treatment including chemotherapy and radiation. Studies show improved outcome is more often observed in patients receiving radiation early in the chemotherapy course. Tannock describes, "The data supports a policy of administering thoracic radiation soon after initiation of chemotherapy for limited stage small cell lung cancer."

Esophageal cancers have been extensively studied with combined chemotherapy/radiation. Protocols comparing radiation alone to radiation with Cis-platin/Fluorouracil chemotherapy was stopped early because of marked improvement in outcome in patients receiving a combined modality therapy.

In colorectal cancer, indications are quite clear. "A National Institute of Health consensus conference has suggested that combined radiotherapy and chemotherapy should be regarded as standard post-operative treatment for patients with rectal cancer."

Similarly, anal cancers are very successfully treated with chemotherapy/radiation, with local control and improved survival rates in the majority of patients, with a treatment that avoids colostomy in most. Tannock notes chemotherapy/radiation gives "equivalent local control and survival to surgery" and has become "the proffered treatment with surgery reserved for local failure."

Tannock suggests "future research might profit from a more individual approach to choosing drugs, based on rapid assays that evaluate mechanisms of resistance or the use of selective inhibitors of tumor repopulation for inclusion in combined modality protocols."

We have established a hot line at 212-CHOICES and e-mail address: gil.lederman@rsny.org. There are also monthly seminars on brain, body and prostate cancer treatment. We invite your participation. We also will ask that you send in copies of films, reports, pathology for review by our panel of experts.