



A New Era of Therapy

Radiation Therapy +/- Chemotherapy with Concurrent Cytoprotection

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Over the last 10 years great strides have been made in the treatment of cancer by combining radiation therapy and chemotherapy. In many instances we have learned that it is better to combine them in a concurrent manner, in order to not only improve local control rates but often improve survival. However, this does not come without consequences, since concurrent radiation therapy and chemotherapy is nearly always more toxic than either one alone or even sequential combined modality therapy.

One of the basic tenets of any form of cancer therapy is that one can modify the therapeutic ratio by either increasing the tumor cell kill or protecting normal tissues from the potentially toxic therapy. Many of the newer and more technologically advanced forms of radiation therapy (i.e., three dimensional conformal therapy, intensity modulated radiation therapy, etc.) permit both the dose escalation to the tumor as well as reducing the volume of normal tissue treated. Another theoretically simple way to increase tumor cell kill is simply by preventing treatment breaks. This has been demonstrated to be true for both chemotherapy and radiotherapy treatment regimens. The final way to improve the therapeutic ratio is by administering agents

which protect the normal tissues from either chemotherapy and/or radiation therapy.

Breakthrough Studies with Amifostine

Clinical studies on the use of amifostine (Ethyol) first began at the National Cancer Institute in 1973. Since then, many studies have been performed which have demonstrated the ability to protect a variety of normal tissues (e.g., salivary gland function, renal function, bone marrow, skin, oral mucosa, esophageal mucosa, testis and many others) from chemotherapy and/or radiation therapy. The key point in understanding the mechanism of action of amifostine is that it is really a pro-drug which is activated at the tissue level by alkaline phosphatase. As a result, the active agent (WR-1065) is actively transported into normal tissues but not tumors. Recently published pre-clinical studies done in monkeys demonstrated this for a variety of normal tissues. This has recently been confirmed by a metaanalysis which demonstrated the lack of tumor protection by amifostine. Other preclinical studies done in rats have demonstrated the necessity for administration of amifostine prior to each daily fraction of radiation.

In the treatment of head and neck

cancers, the usual goal of Cytoprotection is the reduction of acute mucositis and chronic xerostomia. Amifostine is presently the only product listed in the U.S. Pharmacopeia for reducing mucositis related to radiation therapy or chemoradiotherapy. Amifostine is FDA approved to reduce the risks of radiation-induced xerostomia and cisplatin induced nephrotoxicity.

Brizell et al (ASCO, June 6, 2004)

recently updated their results from a randomized Phase III trial of radiotherapy +/- amifostine (200mg/m² slow IV infusion) in the treatment of head and neck cancers. The median time to the onset of grade II xerostomia with radiotherapy alone was 30 days versus 45 days in the patients pretreated with amifostine. The incidence of grade II acute xerostomia was 78% with radiotherapy alone versus 51% in the patients pretreated with amifostine, and the incidence of grade II late xerostomia was 57% with radiotherapy alone versus 34% in the patients pretreated with amifostine. It was also shown that grade II late xerostomia continued to improve out to 24 months post-treatment. There was no difference in locoregional control, progression free survival or overall survival between the two arms of the study. The major side-effects of amifostine were nausea (44%), vomiting (37%), hypotension (15%) and fatigue (10%).

Anne et al (ASTRO 2001) performed a Phase II study of radiotherapy +/- subcutaneously administered amifostine (500mg flat dose) in patients with head and neck cancers. They then compared their results to those of Brizell et al. The median time to the onset of grade II xerostomia with SQ amifostine was 40 days versus 45 days in the patients pretreated with IV amifostine. The incidence of grade II acute xerostomia was 56% with SQ amifostine versus 51% in the patients pretreated with IV amifostine. Furthermore, there was no