Chapter IX: Acute Radiation Effects

Section f: Lung

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Introduction:

Much of the information available on ionizing irradiation acute, sub-acute, and chronic effects on the lung has come from two sources: Clinical Radiation Therapy (1-5) and the reports of pulmonary fibrosis seen in Uranium miners, who inhaled radioactive dust over decades (33).

The physiology and molecular mechanisms of irradiation lung damage follow the complex anatomic and cell biology of the lung. Multiple cell phenotypes interact in both stable and adaptive physiologic roles during normal pulmonary function (6-12). The baseline regulation of the lung inflammatory response represents a major component of pulmonary function (10).

The lung functions to regulate oxygen consumption and expulsion of carbon dioxide. The first information on lung injury came from results of trauma surgery, and thoracic surgery. Pulmonary function tests were designed to define normal, as well as minimally acceptable parameters for survival. These test results are accepted measures of vital capacity (normal volume air movement during an inspiration and expiration) and end expiratory volume (as a measure of capacity of the lung to appropriately collapse during expiration), and is a good indication of the severity of diseases associated with inability to clear blebs, bullae in "air trapping" diseases. The diffusion capacity is a measure of the capacity of cells in the alveolar spaces to carry out appropriate gas exchange. Several categories of pulmonary disease, which are associated with a reduction in lung capacity have been described with patients undergoing trauma surgery and thoracic surgery. The measurements of the survivable relative volume of lung, which is associated with adaptation to loss of pulmonary volume (due to traumatic or planned removal of a lobe, or an entire lung) are used in surgical evaluation of patients. Diseases in which volume of functioning lung is decreased include: removal of infectious lung (tuberculosis or empyema) and lung cancer.

In Clinical Radiotherapy, basic radiobiologic principles of lung volume treated, total radiation dose, fraction size, and total treatment time have been used to establish criteria for safe clinical radiotherapy of lung cancer, esophagus cancer, and various thoracic malignancies such as thymic carcinoma, sarcoma, and thyroid cancer (1-5). Modern radiotherapy techniques with precise isodose-based treatment planning and use of radiotherapy machines, which deliver image-guided, and respiratory-gated treatment fractions now allow precise evaluation of the maximum safe lung volume that can be treated in pre-operative or post-operative protocols for management of lung cancer patients (1-5).

In the 1990's, the advent of 3-dimensional radiotherapy treatment plans made great advances in treatment of lung cancer (1-4). The first decade of the 21st Century included use of Intensity Modulated Radiotherapy (IMRT) (5) and dose volume histograms became routinely used in evaluating a radiotherapy treatment plan for thoracic target volumes. The volume of lung receiving 20% or 30% of the prescribed dose to a tumor volume led clinical investigators to quantitate, and in some cases, predict lung toxicity.

Another new concept in relating radiobiology to clinical radiotherapy is the phenomenon of cardiopulmonary target volume. Data with experimental animals, and clinical outcomes analysis, most recently the RTOG 1708 Clinical Trial and Cross Study showed that the

complexity of the lung, and it's interaction with cardiac volume were responsible to estimate toxicity. In clinical radiotherapy, the concept of cardiac and pulmonary toxicity as a single parameter, has emerged (5). This chapter will focus on the radiobiology of acute, sub-acute, and chronic pulmonary damage as it relates to developing radiation countermeasures. We will also review established parameters for quantitating radiation dose to the lung in the case of inhaled radio-isotopes.

Acute Lung Injury (radiation pneumonitis):

Radiobiology experiments in rodent models (rat and mice) first demonstrated the importance of volume of exposed lung to irradiation toxicity (6-24). The phenomenon of radiation pneumonitis was described in pioneering experiments by Ward and Hill (rat) (29-30) and Travis, Williams, and Franko (mouse model) (25-28). In both rodent model systems, a genetic component to radiation pneumonitis was identified. Not all rodent strains demonstrated the same phenomenon associated with total lung irradiation (endothelial cell swelling, alveolar space replacement with transudates (fluid), and infiltration of the lung with immunocytes (macrophages, lymphocytes, and neutrophils) (24). Basic lung physiology was applied to an understanding of the mechanism of acute irradiation effects in the lung. Diagnostic x-ray evaluation of the irradiated rodent lung showed the "classic" pattern of irradiation pneumonitis, which is associated with replacement of air containing spaces in alveoli with fluid, and appearing white on x-ray films. In animal models, as well as in clinical radiotherapy, the role of circulating inflammatory cytokines was defined following lung irradiation to one lung showed that radiation pneumonitis could develop in the opposite lung. Contralateral pneumonitis could not be explained by internal scatter of radiation outside the target volume and must have been an indirect effect.

The lung (like the oral cavity/oropharynx and intestine) serves as a barrier to entry into the systemic circulation of microbes, toxins, and other pathogens. Ionizing irradiation disturbs the barrier function of the lung acutely by mechanisms common to other barrier organs (31-32). These mechanisms include: the death of dividing cells (in the lung type II pneumocytes), which limit replacement of differentiated cells killed by apoptosis, and depending on dose and lung volume treated, also lead to separation of cell populations, opening of intracellular spaces, destruction of the phenotypes of cells producing protective mucin, and extracellular matrix. Loss of protection by mucin and matrix further disturb the barrier function, and subsequent entry into the pulmonary vasculature of microbes and other pathogens (31-32).

Classic experiments by Ward, et al. (29), and others in rodent models demonstrated the incomplete therapeutic response of radiation pneumonitis to administration of corticosteroids. Some studies, in clinical radiotherapy patients, suffering radiation pneumonitis, demonstrated that administration of corticosteroids could quiet the signs and symptoms of pneumonitis, but following tapering and removal of steroids there was reappearance of radiation pneumonitis, often more severe than the original presentation prior to steroid application. The molecular mechanism of this phenomenon of "recall" of injury is still poorly understood, but relates to the incompleteness of the abrogation of the radiation-induced inflammatory response. Suppression of inflammatory cells by corticosteroids, leads to a reduction in tissue edema, but is not associated with tissue repair, such that removal of the corticosteroids leads to recognition of the original injury and renewed response including recurrent edema and infiltration of inflammatory

cells in response to the dead and dying apoptotic tissue in the lung. Furthermore, administration of broad spectrum antibiotics to attempt to suppress additional secondary inflammation in response to microbes that have entered the tissue, does not prevent the recurrence of signs and symptoms of radiation pneumonitis.

Use of non-steroidal anti-inflammatory agents, or transfer and maintenance of patients with radiation pneumonitis in "germ-free" positive pressure environment is commonly used in acute management of this acute lung toxicity.

There are differences between data from experimental models and human radiation pneumonitis. In particular, work by Richard Hill, et al. (30), demonstrated that sparing of basal volumes in the rat lung greatly reduced pneumonitis compared to sparing similar volumes of tissue in the apex of the lung. Radiation pneumonitis in humans depends more specifically on volume of total lung irradiated, and because of the spread of pneumonitis by circulating cytokines to non-irradiated volumes, may require treatment of radiation pneumonitis based on clinical parameters of infection rather than on lung volume originally treated.

In Clinical Radiotherapy, the volume of lung irradiated, and total treatment time for dose delivery are the most important parameters influencing the incidence and severity of radiation pneumonitis. However, fraction size is also a factor. Depending on the volume treated, daily fractions of greater than 2.0 Gy have been associated with greater severity of radiation pneumonitis (1-5). With the advent of Stereotactic Radiosurgery, (high doses given to relatively small volumes, 10 – 50 cc) irradiation damage to bronchi and central thoracic vasculature, as well as radiation pneumonitis, becomes a dose limiting parameter. The radiotherapy of tumor volumes in the central thoracic cavity requires lower fraction sizes than volumes in peripheral lung.

Acute radiation pneumonitis can also follow inhalation of radioisotopes and has been studied extensively by Jacqueline Williams, et al. (31-32), and laboratory of investigators at Lovelace Laboratories in New Mexico. The quantity of radio-isotopes deposited in the organ, as well as the dose rate of gamma rays beta irradiation and alpha particles, is directly associated with severity of acute radiation pneumonitis. Evaluation of long-lived radio-isotopes such as Uranium 235, Plutonium 239, or Polonium 210, because of low dose rate, leads to less severe acute radiation pneumonitis, but does increase the risk of late radiation effects (fibrosis).

The severity of radiation pneumonitis may be complicated further in patients, who receive total body irradiation (TBI). The use of TBI to prepare recipients for bone marrow transplantation lead to important observations regarding fraction size of TBI, total dose, and dose rate. The use of TBI in bone marrow transplantation has been limited in recent decades, because of the complexity and problem of radiation pneumonitis. Using lung transmission blocks to decrease total dose to lung during TBI was unsuccessful, because of simultaneous shielding of residual cancer or leukemia cells in the patient by these lung transmissions blocks. Otherwise, stated, protecting the lung also protected the cancer. Using twice a day or three times a day small fraction total body irradiation, somewhat decreased the incidence and severity of radiation pneumonitis, but also incompletely prepared the recipient for marrow transplant. TBI has been

largely replaced by use of chemotherapy drugs including: Busulfan, L-Phenylalanine Mustard, Fludarabine, to obviate to the development of radiation pneumonitis.

TBI patients are placed in positive pressure laminar flow rooms, in germ free environments, and are maintained on high doses of antibiotics and anti-fungal drugs to minimize infection from inhaled microbes (31-32). This strategy has been applied not only to allow resolution of radiation pneumonitis, but also to allow time for bone marrow donor cell replacement of the recipient marrow, and stem cell regeneration of polymorphonuclear leukocytes and macrophages to fight infection. However, the toxicity of some antimicrobial drugs can exacerbate radiation pneumonitis. The principles of total volume irradiated (in the case of TBI, it is 100% of lung volume), total dose, fraction size, and comorbid factors (chemotherapy drugs in addition to TBI) may enhance the severity of radiation pneumonitis. Treatment of the radiation pneumonitis patient that is attributable to bone marrow transplant also includes attention to the lung being a possible target for graft vs. host disease. All these issues, require patient isolation, maintenance on antibiotics and antifungals, and in some cases in the case of tachypnea (fast breathing rate) and poor lung function may require intubation and positive pressure respiratory assist. Patients placed on this respiratory support program often cannot recover due to continued weakening of the damaged lung.

Sub-Acute Radiation Damage to the Lung

The definition of sub-acute effects varies between systems and is also subject to significant interpretation when comparing clinical (patient) outcomes of thoracic irradiation with that in experimental animals. In patients irradiated to the thoracic cavity for either pre-operative or post-operative or definitive therapy of lung cancer, the duration and magnitude of acute radiation pneumonitis is dependent upon volume treated, dose, fraction size, overall treatment time, and also depends upon the use of chemotherapy (4-5). Chemotherapy drugs, which are delivered prior to irradiation, can often leave lasting sub-threshold effects, which are brought out when radiotherapy is started. Pushing radiotherapy dose to the full prescribed/indicated dose can produce significantly more lung toxicity than if the patient received no chemotherapy. The magnitude of radiation pneumonitis volume of total lung infected may influence the duration of the acute toxicity. When toxicity subsides by both subjective and objective criteria, the patient is said to have recovered from the acute radiation effects on the lung.

Subjective criteria of acute radiation pneumonitis may be shortness of breath, breathlessness, poor exercise tolerance, and requirement, for example, elevation of the head of the bed for sleeping.

Objective criteria of acute radiation pneumonitis may include breathing rate, requirement for nasal or mask oxygen, often production of sputum, fever, sweating, and in many cases requirement for medical management of this side effect. While steroids are to be avoided, use of non-steroidal, anti-inflammatory agents, and sometimes prophylactic antibiotics are indicated. When both subjective and objective criteria are resolved, this concludes that the patient has recovered from acute radiation side effects. In clinical radiotherapy patients, the definition of sub-acute pulmonary toxicity often includes persistent symptoms and signs of acute toxicity. Otherwise, stated, the acute reaction never totally resolves in patients with poor pulmonary

reserve prior to radiotherapy (Chronic Obstructive Pulmonary Disease, Emphysema, congestive heart failure, and other symptoms and signs of pulmonary hypotension, and asthma) may find that radiotherapy acute effects when combined with these other background medical ailments leads to a situation in which a return to pre-radiotherapy levels of pulmonary function is never achieved. Whether this clinical situation can be described as sub-acute pulmonary toxicity is controversial.

The radiation lung toxicity with rodent and other animal models is quite different from human pulmonary responses (28). Inbred mouse strains show genetic determinants of the acute radiation pneumonitis effect, and the magnitude of what can be called sub-acute irradiation damage (5-22). C57BL/6 mice and C3H/HEN mice both experience acute pulmonary toxicity as described above for animal models; however, the former mouse strain returns to a baseline pulmonary function level including no evidence of histopathology and in assays for irradiation-induced mRNA and inflammatory proteins, return to pre-irradiation levels (23-24). In contrast, C3H/HEN mice never show return to baseline levels of RNA transcripts or proteins for inflammatory cytokines and never completely resolve the objective criteria of acute irradiation pneumonitis. These objective parameters of irradiation damage may remain elevated in C3H/HEN mice, although the mice no longer display signs of acute radiation pneumonitis. Genetic determinants of two different responses are a subject of current investigation. Genetic determinants of a sub-acute radiation toxicity to the lung can be accurately shown in experimental animal models. Carrying out such research in human patients is more difficult because of the confounding variables of: comorbid pulmonary disease, injury, and sometimes active use of tobacco products (smoking), and poly-pharmacy. Patients take medications for other medical conditions, which while unrelated to the disease being treated with radiotherapy or with known elements of radiation reaction, may confound the process of radiation damage healing (31). For example, patients on maintenance chemotherapy or taking immunosuppressive medication for management of a prior organ transplant, medications, which are constantly affecting the healing lung tissues. Because of the above controversies, complexities of the definition of sub-acute radiation damage to the lung, many investigators do not use the term sub-acute radiation damage, but continue to describe the situation as persistent acute radiation reaction.

Readers are encouraged to contact the author of the chapter for discussions and further information (Email addresses are besides the author's name in the Table of Contents.).

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