Management of Toxicities of Combined Modality Therapy for Intrathoracic Malignancies

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**Background:** Combined radiation and chemotherapy for intrathoracic tumors can produce appreciable morbidity. Apprehension about the severity of these toxicities may inhibit optimal patient care.

**Methods:** The literature on recognition, diagnosis, prophylaxis, and management of these toxicities is reviewed and combined with the experiences of the authors to produce management recommendations.

**Results:** Toxicities include acute and chronic esophagitis, early and late pneumonitis with fibrosis, myelosuppression, and neurologic deficits. Measures are available to minimize their severity and to reduce their impact on the patient.

**Conclusions:** The morbidity of combined radiation and chemotherapy patients with intrathoracic tumors can be minimized by recognizing potential toxicities and by applying appropriate prophylactic and management measures.

**Introduction**

Little agreement exists regarding the optimal treatment of patients with locally advanced (unresectable stage IIIA and stage IIIB without pleural effusion) non-small cell lung cancer. Clinical trials in the United States, Canada, and western Europe have compared radiation therapy alone with more aggressive combinations of radiation and chemotherapy, while in the United Kingdom, emphasis has been placed on determining the minimal treatment required for effective palliation of symptoms and comparing “conventional” palliative radiation therapy (24 to 30 Gy in 6 to 10 fractions) with hypofractionated regimens of 1 or 2 fractions. Such differences in research strategy stem largely from philosophical differences regarding the wisdom of treating a large number of patients with aggressive and toxic therapy that will benefit only a few.

The conservative approach recognizes that conventional radiation will rarely produce cures, and impairment of quality of life of patients who receive aggressive concurrent radiation and chemotherapy will be avoided. A more aggressive approach accepts these toxicities in order to improve survival outcomes, either for the majority of patients with extension of median survival or for a subset of long-term survivors. Treatment-related complications may result in substantial morbidity with a decrease in the quality of life. Toxicities encountered in the use of combined chemotherapy and radiotherapy to treat primary lung cancer include esophagitis, pulmonary inflammation and fibrosis, and myelosuppression. Neurologic toxicity is associated with prophylactic cranial irradiation for small-cell lung cancer. Effective management of such treatment-associated toxicities and complications is a challenge. Goals for toxicity management are summarized in Table 1.

In addition to destroying tumor cells, radiotherapy damages normal tissue within the treatment field. Since metastasis in the mediastinal region is present in 70% of lung cancer patients at the time of diagnosis, the treatment plan will include irradiation of the mediastinal lymph nodes and surrounding organs. The effects of radiation tend to occur in tissues whose cells proliferate rapidly, such as those found in the mucosal epithelium. The use of concurrent chemotherapy, particularly with agents that also target rapidly proliferating cells, potentiates the effects of radiation on tissue destruction.

**Esophageal Toxicities**

The esophagus is a muscular structure whose mucosa is comprised of a cell renewal system marked by rapid proliferation. Due to its location near mediastinal lymph nodes, the esophagus usually is included in the high-dose volume during radiation therapy for lung cancer. Radiation effects resulting from inflammation of the esophagus include ulceration, secondary infection, stricture formation, and perforation, and the toxic effects may be acute or late.

Acute effects of radiation therapy are common. They typically occur within two to three weeks after treatment is initiated and may last for several weeks after completion of treatment. Initial symptoms include a sore throat or a feeling of fullness in the throat, which promotes dysphagia. As the treatment course continues, the patient may develop sharp pain along the entire esophagus (or any part of it) and may exhibit symptoms of gastric reflux. Due to tissue inflammation, ulcerations, and the immunocompromised status of the patient, secondary infections of the mucosal lining may occur.

Late effects of radiation therapy to the esophagus, although infrequent, may occur as late as five years after completion of therapy. Esophageal stricture, evidenced by the patient's inability to swallow foods, is the most common late effect. Persistent ulceration, perforation, and fistula formation are rare.

**Management**

Management of esophageal toxicities is facilitated by a multidisciplinary approach. The approach at our institution for management of radiation esophagitis is summarized in Table 2. Acute effects of esophageal tissue damage secondary to intrathoracic radiotherapy historically have been managed with conservative measures, including the use of topical and systemic analgesics and antacids and by the interruption of the radiation therapy itself. Radioprotectors such as amifostine, a thiol compound, currently are under investigation in a phase I pilot study (URCC 1388R). Interruption of radiation therapy to allow acute esophagitis to subside will impair the chances of achieving local control, and such treatment interruptions should be avoided when long-term survival is the treatment goal. Late effects of intrathoracic radiotherapy may require more invasive approaches such as endoscopic dilatation for esophageal stricture.
The goals of symptom management include promoting comfort, decreasing the risk of secondary infections, and maintaining nutrition. Patients undergoing treatment are encouraged to maintain good oral hygiene and minimize further irritation to the mucosal lining. The use of a noncommercial mouth rinse such as warm saline assists in the formation of granulation tissue and promotes healing, and thus should be incorporated into the patients oral care routine.[3] Patients also should avoid using tobacco, alcohol, and hot or spicy foods and fluids because of their irritating effects on the mucosa; tepid food and beverages may be tolerated better and may provide safety from burns in a sensory-impaired oral cavity. Nonnarcotic and narcotic analgesics may be required, depending on the severity of discomfort and pain. A variety of agents such as viscous lidocaine 2%, diphenhydramine, and antacids used alone or in solutions also may minimize the discomfort associated with mucositis and esophagitis. Sucralfate, a nonabsorbable basic aluminum salt of sulfated sucrose commonly used in the treatment of peptic ulcer disease, also forms a protective barrier that promotes healing.[5]

Secondary infection in the mucosal lining often occurs in patients with mucositis and esophagitis. The most common is moniliasis, an infection caused by Candida albicans.[6] Patients who develop fungal infections require treatment with antifungal agents such as nystatin or ketoconazole. The prophylactic use of antifungal agents may be beneficial in high-risk patients.[7]

Since radiation esophagitis produces pain and difficulty in swallowing, nutritional intake may be reduced, thus leading to weight loss. The effects of this dysphagia can last for several weeks after completion of treatment. For mild cases, dietary modifications that incorporate soft, bland foods and those high in protein and calories are encouraged. Nutritional supplements may be added to the diet to enhance protein intake. Patients are instructed to eat small, frequent meals and to avoid items that irritate the mucosa, and those with continued weight loss will require feeding tubes or total parenteral nutrition to maintain their nutritional status. At our institution, vascular-access devices are placed at the time of surgical staging in all patients who are undergoing concurrent chemoradiotherapy for lung cancer to facilitate chemotherapy administration and to provide access for parenteral feeding if needed. While the use of nasogastric tubes that pass through an already irritated esophagus may be more harmful than helpful, these tubes are preferable to parental nutrition for patients who need prolonged nutritional support.

### Pulmonary Toxicity

The majority of patients with lung cancer exhibit compromised pulmonary function from long-term tobacco exposure leading to chronic obstructive pulmonary disease. The extent of pulmonary disease presents challenges in establishing the optimal treatment plan. Complicating the treatment decision is the knowledge that single or multimodality therapy using chemotherapy and/or radiation therapy impairs pulmonary function. The resulting damage may lead to acute or chronic problems that interfere with the patients' quality of life and, in some cases, may cause substantial morbidity.

### Radiation-Induced Pulmonary Toxicity

Although a variety of tissues in the lower respiratory tract tolerate moderate doses of radiation, the lung itself is the major dose-limiting structure in the chest cavity and is highly radiosensitive. Early radiation-induced damage from vascular injury to the small vessels and capillaries throughout the lungs results in vascular congestion and increased capillary permeability. When the vascular injury becomes severe and chronic, arteriovenous fibrillations develops.[8] The loss of lung function resulting from radiation is influenced by factors such as treatment volumes, total dosage, rate of delivery, and the pre-existence of chronic pulmonary disease.[9] Radiation effects on pulmonary function include decreased lung volume and impaired diffusion capacity.[10]

Radiation effects on the lung often are classified as either early (radiation pneumonitis) or late (radiation fibrosis). Both may reflect manifestations of a common set of underlying cellular and biochemical processes.

#### Radiation Pneumonitis

Pneumonitis is an acute effect of radiation-induced pulmonary toxicity that is divided into three phases of radiation response: early, intermediate, and late. Early and intermediate phases of radiation response typically occur one to three months after the completion of treatment and are characterized by swelling and sloughing of endothelial cells of vessels and by increased capillary permeability. Damage to vascular structures causes fluid accumulation in the interstitial tissues and swelling of the basement membrane. Cellular changes in the alveoli result in a denuded epithelium. The alveolar changes produce swelling, cell sloughing, and increased exudate that lead to obstruction of the pulmonary capillaries.[11]

The clinical symptoms of radiation pneumonitis are influenced by the severity and extent of injury to the lung. The classic symptoms of pneumonitis are dyspnea and a nonproductive cough. Fever and night sweats may occur but are unusual. Signs of pulmonary involvement may be unremarkable on physical assessment. Radiographically, infiltration and dense consolidation in the irradiated area are apparent (Figs 1A-D).[8]

The late phase of radiation-induced pneumonitis develops months to years after the completion of treatment. Late effects of lung injury occur when the cells lining the alveoli become hyperplastic and the alveolar walls are infiltrated with fibroblasts.[8] Severe and chronic injury is characterized by sclerosis of the alveolar walls, lumenal narrowing, loss of capillaries, and damage to the endothelium.[11]

Shortness of breath that develops progressively occurs in patients who develop pulmonary fibrosis. Dyspnea and cough may be severe, and the degree of pulmonary compromise may vary. Fever, infection, abscess formation, cyanosis, and clubbing can occur. In severe cases, pulmonary fibrosis may lead to respiratory failure.

The goal of treatment for patients with pulmonary fibrosis is symptom management. If symptoms become intractable, resection of the fibrotic lung may be required.

#### Chemotherapy-Induced Pulmonary Toxicities

Chemotherapy-induced pulmonary toxicities are less common and less severe than radiation-induced effects. The most common significant pulmonary complication in patients undergoing chemotherapy is pneumonitis, which is a consequence of the direct effect of chemotherapeutic agents on the lung. The clinical presentation and radiographic features of chemotherapy-induced pneumonitis are similar to those of radiation pneumonitis. The incidence of chemotherapy-induced pneumonitis is influenced by the chemotherapeutic agent, dose, and route of administration. Some agents are more likely to cause pneumonitis than others, and the risk can be reduced by careful monitoring and prompt intervention when symptoms develop.

A variety of chemotherapy agents are known to cause pulmonary toxicities, including vinca alkaloids, platinum-based drugs, taxanes, and topoisomerase inhibitors. Vinca alkaloids, such as vincristine and vinblastine, can cause acute pulmonary toxicity from direct toxicity to the lung parenchyma. The toxicity is characterized by a nonproductive cough, dyspnea, and chest pain. Lung function tests may show a decrease in forced expiratory volume in one second (FEV1) and diffusing capacity of the lung for carbon monoxide (DLCO).

Platinum-based drugs, such as cisplatin and carboplatin, can cause pulmonary toxicity through their direct effect on the lung. The toxicity is characterized by a nonproductive cough, dyspnea, and chest pain. Lung function tests may show a decrease in FEV1 and DLCO.

Taxanes, such as paclitaxel and docetaxel, can cause pulmonary toxicity through their direct effect on the lung. The toxicity is characterized by a nonproductive cough, dyspnea, and chest pain. Lung function tests may show a decrease in FEV1 and DLCO.

Topoisomerase inhibitors, such as irinotecan and oxaliplatin, can cause pulmonary toxicity through their direct effect on the lung. The toxicity is characterized by a nonproductive cough, dyspnea, and chest pain. Lung function tests may show a decrease in FEV1 and DLCO.

The management of chemotherapy-induced pneumonitis includes supportive care, such as oxygen therapy and bronchodilators, and the use of corticosteroids. Corticosteroids are the first-line therapy for chemotherapy-induced pneumonitis, and their use is guided by the severity of the symptoms and the response to treatment. Other treatments may include bronchodilators, antibiotics, and supportive care.

The prevention of chemotherapy-induced pneumonitis includes careful selection of chemotherapeutic agents, careful monitoring of patients, and prompt intervention when symptoms develop. The prevention of chemotherapy-induced pneumonitis also includes the use of prophylactic antibiotics, the use of prophylactic corticosteroids, and the use of other supportive care strategies.
The effects of chemotherapy-induced lung damage are similar to the effects associated with intrathoracic radiotherapy. Since several antineoplastic agents can cause acute lung reaction, drugs that are used for the treatment of patients with lung cancer must be carefully selected and administered. Drugs that are associated with pulmonary fibrosis when used alone include the nitrosoureas, bleomycin, and mitomycin C. The effects of lung injury secondary to chemotherapy are characterized by vascular damage that results in swelling and fluid accumulation in the alveolar and interstitial spaces. Chemotherapeutic agents cause destruction of type I pneumocytes and hyperplasia of type II pneumocytes. Fibroblastic proliferation can occur and may lead to pulmonary fibrosis.[8] The clinical symptoms that result from drug-induced lung toxicity include dyspnea, fatigue, and a nonproductive cough. The physical assessment is typically unremarkable. Radiographs reveal diffuse infiltrates. Agents that cause a hypersensitivity reaction may reveal bilateral acinar infiltrates that clear.

The development of predictive models for the quantitative extent of pulmonary impairment following radiation therapy to the lung has been difficult.[12-15] The heterogeneity of radiation dose, the variable amount of pre-existing lung damage from both tumor and chronic obstructive lung disease, and the general debility of many patients with lung cancer are complicating factors. Studies of postirradiation lung function in younger patients with Hodgkin's disease may not be applicable to patients with lung cancer.[16] At present, the volume of lung parenchyma and the daily fraction size are key factors in the risk of developing significant impairment.[17]

Clinical Features

Because the development of radiation-induced pneumonitis may cause life-threatening complications, early detection is imperative. The symptoms produced by pneumonitis are typically mild and usually abate in two to four months. Patients with mild presentations of treatment-induced toxicities will require symptomatic management only. Moderate to severe presentations will require a more aggressive approach to prevent the life-threatening complications that can occur.

Patient education is important in the management of pneumonitis. Affected persons are instructed to limit physical activity and are encouraged to perform activities of daily living in small blocks of time by alternating periods of activity with periods of rest. In addition, they are instructed to keep the upper body in an elevated position at all times to promote optimal lung expansion and to improve ventilation. Coughing and deep-breathing exercises are performed frequently throughout the day. The environment is kept well ventilated and free of smoke and other airway pollutants.

Although most patients need supportive intervention only, others require short-term courses of cough suppressants and bronchodilators to alleviate symptoms. Patients who show further progression of the illness require the addition of corticosteroid therapy. Corticosteroids are administered daily for several weeks, and dosage is tapered gradually to avoid the exacerbation of pulmonary symptoms.

In the past, the late effects of radiation - particularly fibrosis - were believed to be relatively fixed entities, and scar tissue, once formed, was considered permanent. However, evidence now indicates that a number of late-radiation and drug effects are more dynamic than previously thought, and even late intervention may modify them. The development of fibrotic changes in the lung is an active process involving the production of a number of inflammatory and fibrogenic cytokines by pulmonary macrophages.[18-20] These processes continue for weeks or months after completion of radiation and thus may provide opportunities for therapeutic intervention.[21,22]

Myelosuppression

Since the chemotherapeutic agents active against small cell lung cancer (SCLC) and non-SCLC produce myelosuppression, the use of hematopoietic cytokines such as granulocyte-colony stimulating factor (G-CSF) and granulocyte macrophage-colony stimulating factor (GM-CSF) has attracted attention to maintain dose intensity and to reduce infectious episodes. While randomized trials have shown reduction in the severity and duration of granulocyte nadirs in lung cancer patients who receive these agents prophylactically, the impact on outcome - whether measured as survival, hospital days for infectious episodes, or cost of infection management - has been modest, and most clinicians avoid their routine use.

Two studies have raised concerns about the concurrent use of thoracic radiation, chemotherapy, and G-CSF or GM-CSF in patients with lung cancer. Momin et al[23] reported two sequential cohorts of patients with non-SCLC treated with thoracic radiation (55 to 65 Gy) and chemotherapy (cisplatin/etoposide/mitomycin C). The first group received no cytokine support, and the second received G-CSF. The mean platelet nadir was significantly lower in those patients receiving G-CSF. Bunn et al[24,25] reported a phase III trial of the Southwest Oncology Group in which patients with limited SCLC receiving concurrent thoracic irradiation (45 Gy/25 fractions for five weeks) and cisplatin/etoposide were randomized to receive or not receive GM-CSF. On interim analysis, it was found that the patients receiving GM-CSF experienced a reduction in granulocytopenia, but they also had more infections, were more febrile, and had more severe thrombocytopenia than those not receiving the cytokine.

The postulated mechanism of these deleterious effects is the killing of circulating hematopoietic stem cells as they pass through the radiation field during daily treatment. To the extent that there is increased mobilization of these progenitor cells by G-CSF or GM-CSF, a blunting or even a reversal of the expected result of the cytokine might occur. Interestingly, similar problems have not been reported with erythropoietin. Presently, the concurrent use of thoracic radiation, chemotherapy, and G-CSF or GM-CSF should be avoided in general clinical practice, and this is reflected in the current American Society of Clinical Oncology guidelines.[26]

Neurologic Toxicity of Prophylactic Cranial Irradiation

In patients with SCLC, failure in the central nervous system (primarily parenchymal brain lesions, but also carcinomatous meningitis and spinal cord compression) is common and increases in frequency as patients live longer.[27] Prophylactic cranial irradiation (PCI) has been praised, damned, and occasionally studied, although few trials have been reported in patients in complete remission at the time of PCI. Survival gains from PCI are modest - approximately a 5% to 10% increase in long-term survival.[28,29] Neurologic disability in patients with SCLC has been attributed to PCI in many reports.[30,31] and a recent review indicates little consensus on the role of PCI concerning the balance between its efficacy and toxicity.[32]

Treatment parameters that are associated with a greater incidence of late neurologic dysfunction include the use of large daily fractions, concurrent cranial radiation and chemotherapy, and treatment with chemotherapeutic agents with some known degree of neurotoxicity (such as methotrexate, procarbazine, and the nitrosoureas).[33] However, most studies have been retrospective and lack reliable information on the baseline neurologic functioning of these individuals. Since these dysfunctions occurred following radiation therapy, they were assumed to be caused by it. Such reasoning, of course, may be fallacious.

Several investigators[29,34-37] have reported careful neurologic assessments of patients with SCLC both prior and following PCI. In general, these reports suggest that, compared with age-matched controls, the testing ability of patients with SCLC is impaired on standard psychometric tests prior to PCI and that further reductions in performance following PCI are modest. It is postulated that at least a portion of the baseline neurologic dysfunction in these patients may be due to paraneoplastic processes. Comparative studies of patients with SCLC and non-SCLC are now underway.[38,39]
The magnitude of benefit achieved with PCI vs the risks of its toxicities remains controversial. While randomized trials have been conducted in Europe, oncologists and/or patients in North America have been reluctant to randomize, with few patients entering an ECOG/RTOG trial of PCI vs observation between 1989 and 1993. Given the current uncertainties, the patient and his or her family should make the choice regarding PCI use after the data on its risks and benefits have been presented. This discussion should be introduced early in the treatment planning rather than after the patient has achieved complete response. To reduce the risk of injury to the brain by radiation and chemotherapy (while recognizing that the damage may be attributed to other reasons), the guidelines proposed by Turrisi[33] - avoiding large fraction sizes, drugs with intrinsic neurotoxicity, and concurrent chemotherapy and brain irradiation - remain appropriate.

Conclusions

Aggressive concurrent intrathoracic radiation and chemotherapy given for locally advanced stages of non-SCLC produces appreciable toxicities. A clearly defined approach to recognition and management of these toxicities will minimize the decrement in quality of life that affected patients will experience. Although the role of PCI in patients with SCLC remains controversial, guidelines are available that will minimize resultant neurologic toxicity.

References
