CRITICAL CARE OF THE CANCER PATIENT

SECOND EDITION

JEFFREY S. GROEGER

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Critical Care of the Cancer Patient

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CRITICAL CARE OF THE CANCER PATIENT

To Karen, Heather, and Elizabeth

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FOREWORD

This book is about critical care medicine as it is practiced at Memorial Sloan-Kettering Cancer Center. Memorial Sloan-Kettering is about caring for cancer patients; the two are intricately intertwined. The rate limiting step in cancer therapy has often been perceived to be normal end-organ toxicity. Surgery, for example, has been limited by the amount of normal tissue that can be resected, radiation therapy by the tolerance of normal tissue within the treatment volume. Systemic therapy has been limited by a myriad of toxicities to virtually every organ system, some of which are unique to the cancer drugs or biologics that are used nowadays in cancer treatment. As a necessity, attempts have been made to overcome these side effects, and as the complexity of these specialized supportive approaches has increased, so has the need for specialists to decide when to deliver them, and, in many cases, special places to deliver them. At cancer centers, critical care medicine and critical care units are unique for the unusual spectrum of clinical syndromes they manage.

There is another unique feature of critical care medicine at cancer centers, and that is the ethical dilemmas posed when we initiate a treatment that has some, but marginal, effectiveness, knowing full well that we may precipitate a long, drawn out process of the treatment of complications that may consume most of the rest of the patient's life and resources. As Dr. Groeger points out in his introduction, the issue is clear for patients who have exhausted all avenues of treatment; heroic efforts and critical care units are not for them. The care they need is palliative; palliative care given with sensitivity and compassion by an experienced medical staff, not to prolong life, but to help the patient leave it with comfort and dignity, either in the quiet of a hospital room, surrounded by family and friends, or at home—not amidst the hustle and bustle of a critical care unit surrounded by blinking lights and beeping machines.

Critical care medicine as presented in this text is the province of the curable. While this seems like an easy distinction, it often is not. Even when complications develop during a patient's initial exposure to a potentially curative treatment, the degree of curability often influences the decision of some physicians to employ and maintain heroic methods of support. How long, for example, do you pursue complex lifesaving methods if the potential for cure, before complications set in, was at best only 10 percent? If the doctor and the patient knew these odds before the treatment was started, should the decision to continue life-saving support methods be different when the complications actually occur? The more common ethical dilemma

is even more delicate and relates to the patient who has failed the first attempt at cure, when the second attempt, the salvage treatment, is new and the end results are unpredictable. Yet in this setting, old treatments often give way to new and better approaches.

Herein lies the danger of too deep a separation between those who initiate treatment and those who administer care in special care units. In the former case, the danger is when the intent to pursue maximum support is based on ancedotal experience; in the latter case, the danger is when the excitement of probing new frontiers is not shared by the critical care specialists. To the cancer specialist, lack of desire to pursue all means of support may seem obstructionist; to the critical care specialist, such care may seem an exercise in the unwise consumption of medical resources. The dilemma is not unlike the potential schism between treatment with curative intent and hospice care. The potential for mistakes is substantial in both directions without the proper communication between specialists. That is why comprehensive, free-standing cancer centers, like Memorial Sloan-Kettering, have a special responsibility. They must keep the treatment specialists, the critical care specialists, and the thanatologists in close contact so that dramatic shifts in opportunities for patients are consistently communicated. The key is in the shared experience and the shared decision making—the decision to treat or not to treat.

In the past 20 years, critical care medicine has emerged as a specialty in its own right, paralleling improving trends in cancer treatment. Cancer surgery has become less radical, radiotherapy more precise and less toxic because the normal treatment volume has become smaller, and chemotherapy less empiric, more effective, and less toxic. More cancer patients are alive and well as a result. This has, however, increased the complexity of the decision of when to employ critical care facilities, but this problem is a welcome substitute for what we had; and this text is a welcome addition to this complex area.

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INTRODUCTION

Few words evoke a visceral response as dramatic as does 'Cancer.' Is this fear rational? Childhood lymphoblastic leukemia, Hodgkins' disease, choriocarcinoma and testicular cancer, once fatal diseases, are now curable. Bone marrow transplantation, monoclonal antibodies, interleukins, interferons and tumor necrosis factor, interstitial radiation therapy, and continual evaluation of new single and multiple agent chemotherapy regimens offer hope to otherwise despondent patients with rapidly fatal neoplasms. Yet we are all too aware of the toxicity and potential lethality of antineoplastic therapy even when cure is attainable.

Intensive Care Unit intervention is life saving in cases of acute reversible diseases such as drug overdose or major trauma. For the patient with malignancy, the role of Intensive Care Unit management is less well defined. What then are the indications for admitting cancer patients to the ICU, and what is optimal care?

Reliable predictors of ICU mortality are few for the general patient population, and are virtually nonexistent for patients with malignancies. At the Memorial Sloan-Kettering Cancer Center ICU, prospective patient survival probabilities are derived daily using logistic regression which incorporates Therapeutic Intervention Scoring System (TISS), Pa_{O_2}/Fi_{O_2}, and creatinine clearance. This data allows us to discuss prognosis with physicians and family members independent of the patients primary malignancy. However, it cannot predict which individual will benefit from aggressive ICU care prior to admission.

ICU admission should ideally be based upon the probability of survival, and the anticipated duration of life after discharge, providing the patient wishes to receive extraordinary life-support. Considering the issue in this light, it is inconsequential whether a patient, admitted to the ICU with an acute life-threatening complication, has no underlying disease, or has suffered for years from chronic respiratory disease, or has a malignancy. Each of those conditions will affect the estimate of recovery and survival, and will be automatically factored into any decision based on ultimate outcome. Limits and objectives of intensive care must be discussed objectively between the critical care physician, oncologist, and patient at this stage.

Patients suffering from complications of an initial course of aggressive cancer therapy, no matter how serious the conditions, should almost always be considered for ICU admission if there is reasonable hope that the treatment employed may stop or reverse the progression of the malignancy, and the patient wishes aggres-

sive Intensive Care Support. As an example, although the mortality of respiratory failure requiring mechanical ventilation developing in individuals with hematologic malignancy is exceptionally high (65% to 90%), cure of the malignancy may be achieved if remission is obtained, and bone marrow transplantation is available. On the other hand, a patient with a terminal illness with no further therapeutic options in which ICU support would only prolong a death may not be a candidate for admission, even when the immediate problem has a reasonably good prognosis.

The advances we have seen in our attempts to cure cancer have not come without cost. Immunosuppression, opportunistic infections, metabolic perturbations, and organ dysfunction related to the primary disease or its therapy can all be life threatening. An understanding of those processes by the critical care physician independent of his expertise in the management of organ failure is mandatory when caring for the cancer patient. As the Critical Care Team must understand the prognosis of the primary malignancy as they evaluate patient for ICU admission, the oncologist must be aware of the exceptional lethality of multisystem organ failure independent of the neoplasm.

Critical Care of the Cancer Patient is not intended to be a general text on ICU management or Oncology, but rather focuses on special diagnostic and management issues as they relate to problems seen when caring for the cancer patient. The text represents a management approach of authors whose charge is to care for, investigate, and hopefully cure patients with cancer. No attempt is made to seek unanimity amongst contributors in management, but rather to develop approaches based on pathophysiology and clinical experience.

Until validated preadmission predictors of ICU outcome are available, physicians must use their best clinical judgment to decide levels of care and duration of support. Through the work of many devoted patients, physicians, and nurses willing to "fight the odds," many fatal malignancies are now curable. We hope this text lends to continued improvement in cancer outcome and quality of life.

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CONTENTS

CHAPTER 1

Acute Toxicities of Cancer Therapy

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Because anticancer therapies affect the growth of proliferating tissues, we can usually predict the type, timing, and severity of the adverse effects they can cause. Myelosuppression, a common side effect, occurs days or weeks after the drugs are administered. Effective management strategies are readily available to anticipate and treat this complication. Although rare, acute toxicities do occur. Unlike other side effects, they require rapid recognition and treatment and occasionally support in an intensive care unit. This chapter discusses the diagnosis and management of immediate toxicities of anticancer therapy affecting the heart, lungs, and gastrointestinal tract. It also examines hypersensitivity reactions associated with cancer treatment.

CARDIOPULMONARY TOXICITIES

Patients with cancer can develop cardiopulmonary decompensation from any cause including intrinsic heart disease; tumor involvement of the heart, pericardium, or lung; pneumonia, and other infectious complications. The incidence of these problems is increased in patients treated with anticancer therapies. Most patients who experience side effects develop chronic toxicity such as congestive cardiomyopathy with doxorubicin and daunomycin, and pulmonary fibrosis with bleomycin and mitomycin. Acute complications of therapy are uncommon, but nonetheless important in the differential diagnosis of cardiopulmonary deterioration of the patient with cancer.

5-Fluorouracil Cardiotoxicity

5-fluorouracil (5-FU) is used in the treatment of breast, gastrointestinal, and head and neck cancers. Common side effects include myelosuppression, mucositis, vomiting, and diarrhea.[1] Cardiotoxicity associated with 5-FU, manifested as myocardial ischemia, was first reported in 1975.[2] In 1982, 1,083 patients receiving 5-FU were reviewed and the overall incidence of myocardial ischemia was found to be approximately 1.6%. The risk of cardiotoxicity was greater in patients with a previous history of ischemic heart disease[3] and also more commonly seen in patients receiving continuous infusions of the drug. In one report, 3 of 36 patients receiving continuous infusions of 5-FU developed myocardial ischemia while no cardiac toxicity was recognized among 120 patients who received bolus doses of the drug.[4]

Patients develop acute retrosternal chest pain within several hours of beginning 5-FU, in most cases after the second or third dose of the drug. When the drug is readministered, the pain usually recurs. The electrocardiogram most commonly reveals changes consistent with ischemia. In some cases, the syndrome has occasionally been associated with myocardial infarction and death.[5] Patients respond clinically to nitrates and discontinuation of 5-FU.

The cause of 5-FU cardiac toxicity is not known. That cardiac ischemia is the underlying pathophysiologic condition is supported by the clinical features, associated ischemic changes on the electrocardiogram, the recurrence of symptoms when the drug is administered, the response to nitrates, and the occasional association with myocardial infarction.

Acute Dyspnea Following Mitomycin and Vinca Alkaloids

Combinations of mitomycin and vinca alkaloids have come into wide use to treat patients with breast, ovarian, and non–small-cell lung cancers. Pulmonary fibrosis associated with mitomycin has been described.[6] The vinca alkaloids (vincristine, vinblastine, and vindesine) when used alone have not been associated with any pulmonary reactions. However, sev-

eral cases of acute respiratory symptoms have subsequently been described in patients receiving both mitomycin and vinca alkaloids.[7–9] We have reported a series of 25 patients with non–small-cell lung cancer who developed the syndrome of acute respiratory distress while receiving a combined mitomycin and vinca alkaloid chemotherapy program, with an overall incidence of 4%.[10]

In all patients, the syndrome occurred on the day that either vindesine or vinblastine was administered. Some patients had also received mitomycin on the same day, and all had received it in previous cycles.

In the majority of cases, the episodes occurred 1 to 2 hours after administration of the vinca alkaloid (range 45 minutes to 3.5 hours), most frequently after the third dose of mitomycin (range 2–5 doses) and after a median of ten doses of the vinca alkaloid (range 7–15 doses).

The syndrome is characterized by acute dyspnea without cough, sputum production, hemoptysis, or chest pain. The physical examination in all cases reveals tachypnea. Bilateral rales or rhonchi are seen in 31%, and wheezing in 37%. Hypotension is not noted.

In most cases the arterial blood gas analysis reveals an oxygen partial pressure (Po_2) of less than 60 mm Hg. An elevated white blood cell count and eosinophilia are not seen. The chest roentgenograms most commonly reveal bilateral interstitial infiltrates. Localized infiltrates were noted in two cases. Electrocardiograms do not reveal ischemic changes.

Clinical resolution of the acute syndrome occurs in all cases within 12 hours. Patients have generally been treated symptomatically with supplemental oxygen and bronchodilators. Some patients received intravenous (IV) boluses of corticosteroids. Only 1 of 25 patients required mechanical ventilation.

Dramatic clinical improvement is expected in all patients by 24 hours, and chest radiographs commonly show complete resolution. Some patients, however, develop progressive dyspnea, which may be associated with persistent radiographic abnormalities. These patients often require chronic corticosteroid therapy. Lung function tests in these patients show the development of an interstitial defect such as that seen with mitomycin toxicity.

The etiology of this acute dyspnea syndrome associated with mitomycin and vinca alkaloid therapy is not known. In patients who have been rechallenged with vinca alkaloids, the syndrome recurs. Both mitomycin and vinblastine must be discontinued if the syndrome occurs.

Cyclophosphamide Cardiomyopathy

Cyclophosphamide is a chemotherapeutic agent whose side effects include myelosuppression, nausea and vomiting, and hemorrhagic cystitis.[11] When administered in high doses (120–240 mg/kg) such as those used in bone marrow transplantation, cyclophosphamide can cause hemorrhagic myocardial necrosis.[12, 13] The effects are dose-related but do not appear to be cumulative. The incidence of this complication is not known.

Congestive cardiomyopathy associated with cyclophosphamide occurs acutely with death occurring within 2 weeks after the last dose of the drug. Electrocardiographic changes include loss of R waves and ST-T wave changes. Serum elevations of creatine kinase (CK), aspartate aminotransferase (AST), and lactic dehydrogenase (LDH) may be seen. Radiographs show changes consistent with pulmonary edema.

Risk factors for cyclophosphamide-associated cardiotoxicity are not well delineated. Patients receiving doses in the range of 120 to 240 mg/kg should have careful cardiac monitoring, including serial electrocardiograms to assess voltage and echocardiography to evaluate left ventricular function.

Bleomycin Chest Pain

Bleomycin occupies a major role in the therapy of germ cell cancer and lymphoma.[14] Sites for preferential drug distribution and toxicity include the skin and lung.[15] Pulmonary toxicity is manifested by interstitial pneumonitis leading to fibrosis. Pulmonary fibrosis, reported to occur in 3% to 4% of patients, is not only the most serious complication but also potentially fatal.[16]

Severe chest pain can occur in patients receiving continuous bleomycin infusions.[17] The syndrome is characterized by the acute onset of severe chest pain described as either retrosternal pressure or pleuritic-like pain occurring on the second or third day of the infusion. The severity of pain suggests myocardial disease or pulmonary emboli. Associated symptoms of cough and dyspnea were rare. Hemoptysis was not noted. Chest roentgenograms were without acute changes. Some patients had electrocardiographic changes consistent with pericarditis. After the infusion was discontinued, symptoms resolved in all cases. A decrease in the infusion rate also led to clinical improvement. No long-term sequelae were noted.[17]

The syndrome is uncommon, with a reported incidence of 2.8%. The pathophysiology is unknown; however, the possibility of serosal inflammation manifesting as pleuropericarditis is likely.

When chest pain develops during the infusion of bleomycin, it may be treated with analgesics or by slowing the rate of infusion. If the pain persists or is associated with electrocardiographic changes, the drug should be discontinued. Further bleomycin is not contraindicated, and pulmonary complications are not expected.

Interleukin-2

Interleukin-2 (IL-2), a glycoprotein produced by activated human T cells, is a potent modulator of immune responses. The administration of IL-2 alone or in combination with immune lymphoid cells activated by incubation with IL-2 has been reported to produce anticancer effects.[17, 18]

Limiting acute toxicities of IL-2 include hypotension, pulmonary edema, azotemia, creatinine elevations, confusion, disorientation, and agitation. Recently, arrhythmias have been reported.[19] Complications of IL-2 have been shown to be dose-related and reversible after treatment has been stopped.[19]

Nearly all patients develop hypotension, which initially can be managed with IV fluids. Weight gain of 10% of body weight is seen in 50% of patients. With continued administration of IL-2, capillary permeability is increased and most patients require vasopressors to maintain blood pressure.

Pulmonary edema owing to increased capillary permeability occurs in at least 20% of patients treated with IL-2. Clinically, dyspnea at rest associated with arterial oxygen desaturation occurs which may respond to diuretic therapy. When pulmonary edema occurs, the IL-2 infusion must be discontinued. Approximately 5% of patients will require mechanical ventilation and some develop progressive lung disease resembling the adult respiratory distress syndrome.[19]

Some patients can develop supraventricular tachycardia and occasionally ventricular tachycardia requiring cardioversion. In addition, retrosternal chest pain, ischemic electrocardiographic changes, and myocardial infarction, which may be fatal, have been reported.[19]

Toxicities of Il-2, including hypotension, pulmonary edema, oliguria, and cardiac arrhythmias, are dose- and time-related and usually reversible following cessation of the drug. Significant morbidity is associated with this therapy, often requiring intensive care–level support.