Chemotherapy in Carcinoma of the Lung*

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Impressive gains in the treatment of a variety of hematopoietic malignant diseases, acute leukemia, Hodgkin’s disease, and the non-Hodgkin’s lymphomas, and in certain solid tumors, such as carcinoma of the breast, have been made in the past two decades by chemotherapy. Unfortunately, until recently, cancer of the lung has not been the object of similar intensive investigations into chemotherapy with multiple-drug regimens or combined-method therapy. Although there is reason for guarded optimism in the management of cancer of the lung, let us begin with some relatively dismal facts.

Although single agents have been used in extensive trials to treat cancer of the lung, there has been no significant benefit with respect to prolongation of life or reduction of morbidity in this disease utilizing these single agents. Extensive studies on large numbers of patients by the Veterans Administration and other cooperative study groups have failed to demonstrate significant benefits in treating cancer of the lung; however, in many of these studies, two very important elements have been overlooked when these statistics are emphasized.

First, all lung cancer is not identical, and it has recently become extremely important to identify the histologic type of lung cancer in order to plan appropriate therapy. Not only are the histologic types different in their natural evolution, but these differences are extremely important in the determination of the response to chemotherapeutic agents, radiotherapy, surgery, and, indeed, immunotherapy. Physicians should avoid the general term, “lung cancer,” and begin to speak of the following major histologic types: epidermoid (or squamous); small cell anaplastic; large cell anaplastic; adenocarcinoma; and not otherwise classifiable anaplastic tumors. The response of these tumors to therapy is very different. Small cell anaplastic carcinoma has an extremely rapid doubling time and is initially responsive to many chemotherapeutic agents but probably is disseminated in most instances from the time of its initial recognition. Most modern therapeutic programs for the management of small cell anaplastic carcinoma recognize these facts and treat this type of lung cancer as a distinct entity. It is therefore necessary to recognize the importance of adequate histologic classification in discussing the results of the treatment of lung cancer.

Secondly, although the length of survival of patients with lung cancer is not statistically enhanced, certain forms of lung cancer are responsive to chemotherapeutic agents. Small cell anaplastic carcinoma has shown responses to a wide variety of single agents and to many multiple-drug regimens of chemotherapy; however, the length of response is short, and with relapse the patient usually cannot be induced to remission. Survival has not been enhanced by single-agent chemotherapy, although the use of multiple-agent chemotherapy has provided some small statistical increase in life span.

The successes with multiple-agent chemotherapy in the management of carcinoma of the breast and the hematopoietic neoplasms has led to the investigation of such combined therapy in lung cancer. Multiple-agent chemotherapy has proved particularly successful in two histologic types of lung cancer, small cell anaplastic carcinoma and disseminated epidermoid or squamous cell carcinoma. These two histologic types have appeared to be responsive to several multiple-drug regimens of chemotherapy. A number of different combinations are in current use and are being evaluated. Two features common to successful chemotherapeutic programs have included (1) the combination of agents that have shown some activity singly in at least one histologic type of carcinoma of the lung and have different pharmacologic actions and toxicities, and (2) the use of drug scheduling, that is, the use of drugs active at different points within the cycle of cell division which are administered in a fashion to potentiate their cytotoxic activity.

The use of the Vinca alkaloid, vincristine, with the antitumor antibiotic, bleomycin, has proved to be a particularly valuable combination. Evidence from the laboratory suggested that the sequential administration of vincristine followed by bleomycin would prove effective in both small cell anaplastic and epidermoid carcinoma of the lung, and there is clinical evidence from several cooperative trials to substantiate these data from the laboratory. The use of this technique of drug scheduling provided for the first time a combination of drugs to which epidermoid carcinoma was responsive. The initial reports on the use of the chemotherapeutic program entitled “COMB” (cyclophosphamide, vincristine sulfate [ Oncovin], methyl CCNU, and bleomycin) were substantiated at a somewhat lower rate of remission by pilot studies done in several cooperative groups.
Such combinations were capable of causing some regression of the tumors in approximately half of the patients with disseminated epidermoid carcinoma, and in approximately 15 to 20 percent of these patients, a significant prolongation of the life span could be obtained; however, this is a relatively small fraction of the patients with disseminated epidermoid carcinoma.

Patients with anaplastic small cell carcinoma were also responsive to the multiple-drug program, with objective regression seen in 60 to 65 percent of these patients and with a statistically significant, although brief, prolongation of life demonstrated in this group. Patients with small cell anaplastic carcinoma of the lung were also exquisitely sensitive to other combinations which included alkylating agents, vincristine, and doxorubicin hydrochloride (Adriamycin). The antibiotic, doxorubicin hydrochloride (Adriamycin), in combination with an agent with alkylating properties, hexamethylmelamine, has also proved to be effective in the management of both small cell anaplastic and epidermoid carcinoma (S. A. Armentrout, MD, unpublished data). Recent reports from the M. D. Anderson Hospital would suggest that combination including bleomycin, doxorubicin hydrochloride (Adriamycin), nitrogen mustard, vincristine, and mechlorethamine (nitrogen mustard) may show excellent activity in these histologic types.

Recently, drugs such as hydroxyurea and methotrexate have been employed in an attempt to recruit tumor cells into the mitotic cycle and to increase the "kill" of tumor cells by cycle-active drugs such as cytarabine (cytosine arabinoside). A number of encouraging results have been obtained in the laboratory with these combinations of drugs, and they should shortly be available for clinical trials in lung tumors of man.

In general, chemotherapeutic combinations have been inactive in primary adenocarcinoma of the lung and large cell anaplastic carcinoma of the lung. No effective single agents or multiple-drug combinations have been demonstrated to be effective in treating these types of tumors; however, it is important to recognize that the adenocarcinoma may be metastatic to the lung. In women, metastatic carcinoma of the breast has proved extremely responsive to combinations of chemotherapeutic agents, particularly those including an alkylating agent, methotrexate, and 5-fluorouracil. There is some suggestion that primary adenocarcinoma of the lung and large cell anaplastic carcinoma of the lung may be responsive to combinations of drugs including procarbazine and the antitumor antibiotic, doxorubicin hydrochloride (Adriamycin). Procarbazine, either alone or in combination with 5-fluorouracil, methotrexate, or an alkylating agent, has been able to induce remissions in small series of patients with these resistant histologic types.

There are several areas of recent activity in the application of chemotherapy to cancer of the lung. Progress must be made into these areas before any effective chemotherapeutic program can be designed. Of particular importance is the ability to induce remissions in primary adenocarcinoma, large cell anaplastic carcinoma, and undifferentiated carcinoma of the lung. At the present time, no successful programs for inducing such remissions are available. Also, a program of treatment must be found that will increase the low initial rate of response in the largest histologic type of carcinoma of the lung, ie, epidermoid carcinoma. Although significant rates of remission in the order of 20 to 25 percent are being obtained by currently available chemotherapeutic programs, this still does not represent a satisfactory initial rate of remission. Together with programs for increasing the initial response in epidermoid carcinoma, methods are needed to prolong remissions. Although some patients with epidermoid carcinoma have significant remissions following chemotherapy, the overall benefit in "quality of life" remains poor. Despite the fact that the initial rate of remission with chemotherapeutic agents is good in small cell anaplastic carcinoma of the lung (up to 60 to 65 percent), there is an acute interest in prolonging the duration of these often rather short remissions. The rate of relapse in this histologic type is high, and the duration of remission frequently is extremely short. A variety of chemotherapeutic, immunologic, and combined-method programs are being investigated to attempt to maintain the disease-free interval.

Several areas of recent active investigation have been alluded to previously in this report. First, drug scheduling has been shown to be of increasing importance in treating cancer of the lung. The use of active agents in random combinations is no longer adequate, and the laboratory investigations that identify the precise sequence and timing of multiple-drug regimens are proving of great importance. Secondly, the use of chemotherapy, radiotherapy, and immunotherapy as adjunctive treatments, particularly in early cancer of the lung, will come under intense investigation in the near future. In both early and advanced stages of cancer of the lung, the use of chemotherapeutic agents in combination with radiotherapy has rather dramatic effects in potentiating the tumoricidal effect of each agent. The enhancement of radiotherapy by chemotherapy may provide a significant new dimension in the management

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of tumors of the lung. Lastly, immunotherapy may be of benefit in tumors of the lung, both in the induction of remission when the burden of tumor is small and also in the prolongation of remission following conventional therapy. Each of these methods is being explored in an attempt to provide an increased number of remissions and significant prolongation in the quality of life for patients with cancer of the lung.

REFERENCES

Immunologic Aspects of Lung Cancer*

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Surgeons are often puzzled by variations in the natural history of lung cancer. Some patients with large neoplasms of borderline resectability may survive for many years after surgical treatment, whereas others with smaller, easily resectable carcinomas die from disseminated metastatic disease within a few months. The occasional success encourages the surgeon to treat lung cancer, but it is obvious that any improved survival in patients with lung cannot come from further progress in surgical therapy.

The purpose of this presentation is to review some of the reasons why the use of surgical therapy alone often results in failure of treatment; these reasons are reviewed in the light of newer concepts of the basic immunobiology of lung cancer.

Surgery for cancer is based upon the concept that cancer begins as local disease that spreads in an orderly fashion from the primary site to adjacent tissues by direct extension to regional lymph nodes via the lymphatic and the blood vessels. The surgical procedure is designed to remove the primary neoplasm and the usual contiguous routes of spread. Theoretically, the aim of surgery is to remove every last cancer cell from the body. Advances in surgical techniques, anesthesia, and supportive care have permitted the development of progressively radical, extensive surgical procedures. Unfortunately, these more complex procedures have failed to increase the rates of cure for lung cancer. In fact, for the past several decades, there have been few significant improvements in the management of lung cancer by surgery alone, and it is doubtful that surgical techniques, as practiced today, can contribute to increased survival.

Because lung cancer is the leading cause of death from cancer in the United States today, it is perhaps worthwhile to explore some of the reasons behind these failures. First, it would appear that many of the assumptions upon which the principles of surgery for cancer were based are, in fact, inaccurate. We are particularly concerned with the concept that the surgeon cures the patient by removing, with his surgical resection, every last tumor cell. We know, for a fact, that this is not the case, because many patients in whom one finds tumor cells in the washings of surgical wounds, in the lymphatic vessels draining a primary tumor, or even in the circulating blood, have been “cured” by surgical resection. If these findings are correct, then we must assume that the operation has influenced the host-tumor relationship in some way.

Recent reports describing the relationships between the host’s immune defenses and the growing neoplasm suggest that the growing tumor can invade the host’s immune responses in order to facilitate its own growth. We suggest that the surgeon’s major role in many cases is to remove the bulk of the tumor, which lowers this level of immunosuppression, both specific and nonspecific, induced by the neoplasm and allows the host’s immune defenses to recover sufficiently to destroy the microscopic foci of