Clinical Experiences with Chemotherapy for Carcinoma of the Lung

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The actual statistical increase in the incidence of bronchogenic carcinoma during the past decade has been most alarming. Despite attempts at raising the salvage rate of patients with cancer of the lung by a more aggressive and radical surgical approach, the overall end results show a survival rate which leaves a great deal to be desired.† Until approximately five years ago little could be offered to the patient with inoperable bronchogenic carcinoma, other than intensive radiation therapy. Up to the present, this has not succeeded in prolonging the survival time. In many instances, radiation therapy produces unpleasant side effects such as pulmonary fibrosis and destruction of the lung with consequent dyspnea and pulmonary incapacitation. During the past five years, a great deal of interest has been stimulated in cancer chemotherapy. In the national program, some 40,000 drugs have been screened and of this number, 100 have been deemed suitable for use in the human being. Approximately 20 of these have received clinical trial.‡ Generally speaking, early impressions would seem to indicate that the chemotherapeutic attack upon carcinoma of the lung has produced some encouraging results in terms of palliation and perhaps even in some instances has resulted in the prolongation of life.

Response and Side Effects

It is to be remembered that chemotherapeutic drugs must be used with the greatest of caution as they are extremely active compounds which can produce serious toxic effects. In most instances these drugs are given up to the point of tolerance in an effort to achieve major therapeutic responses. Host resistance or natural immunity can be seriously depleted if one gives too much of a highly toxic drug. When this occurs, the patient may actually have an increase in the tumor size or even spread.§ Experiences would indicate that the most common side effects to be expected are leukopenia, nausea, vomiting, diarrhea, enteritis and perhaps alopecia. In practically all cases, fortunately, these toxic side effects have been reversible.

Choice of Chemical Agents

Our clinical experience has been limited to the following cancerocidal agents which generally speaking fall into two main categories.

1. Alkylationg agents which owe their primary effectiveness to the interference with proliferation of rapidly dividing cells. Alkylation agents used in this report included mechloretamine hydrochloride (HN6) or nitrogen mustard, thiopeta, chlorambucil and cyclophosphamide or cytoxan.

2. Antimetabolite agents which interfere primarily with the deoxyribose nucleic acid and ribose nucleic acid synthesis in the cells. Our experience has been limited to two antimetabolites; methotrexate and 5-fluorouracil used in conjunction with x-ray radiation therapy.

Methods of Administration

In the past, we have experimented with several routes of administration of the cancerocidal agents in the management of primary and metastatic carcinoma of the lung.

At the present time, it is questionable whether regional perfusion with high doses of chemotherapeutic agents is the choice

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method of treating carcinoma of the lung because of leakage hazards which can result in serious if not irreversible bone marrow depression. Recent animal work, however, has demonstrated that very high doses of nitrogen mustard can be perfused through the animal lung with low leakage. In the same animals it was obvious that local tissue tolerance remained an important controlling factor in the amount of agents that can be introduced by this method into isolated lung tissue.

1. **Intra-arterial administration.** It is possible to administer much higher doses of chemotherapeutic agents into both the pulmonary artery and the pulmonary vein in the operating room during open chest procedures. We have felt some degree of security in this approach in the past because of the very rapid and early fixation of the agent in the tissues within short intervals of 15 minutes to one hour. Originally it was our intention to sterilize the lung-and the general systemic circulation to dispose of all circulating cancer cells. This procedure was carried out in a total of nine patients. This approach has been discontinued because of the very obvious hazards of bone marrow depression, and the sudden lowering of local tissue tolerance with a high incidence of necrosis, hemorrhage and chemical pneumonitis. In the management of carcinoma about the neck, pharynx and oral cavities we still prefer direct cannulation with plastic catheters in the arteries supplying the area followed by the administration of very high doses of cancerocidal agents. This has resulted in gratifying rapid decrease in the size of the tumor and in many instances the healing of an open cancer ulcer which in the past has remained refractive to all other types of therapy.

Catheterization of the pulmonary artery in a manner similar to that ordinarily employed in routine right heart catheterization has also been utilized as a method of administering very high doses of cancerocidal agents into the pulmonary artery. The cardiac catheter in four instances has been allowed to remain in place for intervals between ten to 14 days. In all instances when the concentration of the cancerocidal agents is raised to desirable levels there has been a resultant chemical pneumonitis with severe toxemia, fever and x-ray changes showing lobar consolidation. In general our experiences would indicate that the intra-arterial administration of the cancerocidal agents has little to recommend it in the management of carcinoma of the lungs. We still prefer this method of therapy in the management of neoplastic lesions about the neck, pharynx and oral cavity.

**Criteria for Determining Improvement**

We generally have used the following criteria for determining improvement in patients receiving chemotherapy for carcinoma of the lung.

1. A measurable reduction in the size of the tumor within an interval of three months after the institution of therapy.
2. Symptomatic improvement.
3. General improvement in the patients' physical status and his ability to return to some type of gainful occupation.
4. Gain in weight.

**Results**

During the past four years some 450 patients with carcinoma involving one of the numerous body systems have received chemotherapy. Included in the group have been 76 patients with primary or metastatic carcinoma of the lung. Seventy-two patients have had primary cancer of the lung. Four patients were treated for metastatic breast carcinoma involving the pleura and/or lung. Twenty-six (34 per cent) of the 72 patients with primary carcinoma of the lung showed significant clinical improvement by the criteria we have outlined.

We have been particularly impressed with the rapid response of patients with su-
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Figure 1A: Large carcinoma of thymus involving entire mediastinum. Figure 1B: Angiogram shows total obstruction of superior vena cava by thymic tumor. Figure 1C: Complete disappearance of tumor following treatment with thoracotomy and x-ray therapy.
perior vena caval obstruction due to primary carcinoma of the lung following therapy with nitrogen mustard. Complete clinical relief has been experienced within 24 to 36 hours after the institution of therapy. 5-fluorouracil, an antimetabolite, when used in conjunction with x-ray radiation therapy offers distinct future promise as a combined method of therapy. In one instance, a highly malignant thymoma, a type of lesion which does not ordinarily respond to any type of therapy, showed a very excellent and rapid response to combined 5-fluorouracil and x-ray radiation therapy. There was complete clearing of a total pretreatment vena caval obstruction (Fig. 1 A, B, C). When combined 5-fluorouracil and x-ray radiation therapy is employed the necessary x-ray tumor dose is remarkably reduced to either one half or one fourth that ordinarily necessary to obtain a comparable result with x-ray treatment alone.

Chlorambucil by the intravenous or oral route and cytoxan by the intravenous route gave uniformly the best results. These two agents were used in the majority (58) of the patients with primary carcinoma of the lung.

In two instances very large carcinomas of the lung which appeared inoperable by x-ray examination were treated preoperatively with intensive chemotherapy. Both were subsequently explored. In one instance it was definitely the feeling of the operator (FLM) that the dissection of the mediastinum was much easier than in those instances where the primary cancer had received preliminary preoperative x-ray radiation therapy. In both instances the preoperative chemotherapy resulted in appreciable reduction in the size of the carcinoma mass and general systemic improvement in the patient.

Experiences in the past have demonstrated that the small-cell type of bronchogenic carcinoma usually results in the most extensive spread and has the lowest operability and resectability rate with very few if any cures. Two patients in this series had small cell undifferentiated carcinomas treated by lobectomy followed by postoperative adjuvant chemotherapy. One patient is alive and well one year and ten months following operation (Figs. 2A and B). The second patient is doing well one year after operation. These experiences would suggest that the better postoperative survival rate with the small-cell type of carcinoma is the result of sterilization of the blood stream and the "cancer cells" which would otherwise remain dormant for months or years. It is our impression that perhaps the greatest value of adjuvant

**Figure 2A**  Undifferentiated carcinoma involving right upper lobe lung. **Figure 2B**  Same patient one year and ten months following lobectomy and adjuvant chemotherapy.
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Chemotherapy is in the pre- and postsurgical treatment of patients with primary carcinoma of the lung particularly if the cancer is of the undifferentiated small cell variety. Some caution, however, must be exercised when chemotherapy is used in conjunction with operation. Lowered host resistance in the immediate postoperative period may result in poor healing of the bronchial stump, prolonged convalescence and in some instances poor wound healing. It is our experience that the chemotherapeutic agents cannot be pushed to the same toxic level in the postoperative patient as is ordinarily employed in the patient who has not been treated by surgical removal of the carcinoma.

In the four patients with metastatic breast carcinoma involving the pleura and lung the results were uniformly gratifying. In one instance (Figs. 3A and B) a 54-year-old white female patient who had metastatic carcinoma involving the pleura and lung as demonstrated by thoracotomy and biopsy is alive and well two years and four months after the institution of chemotherapy.

Three patients considered to be terminal showed remarkable improvement after treatment with chlorambucil. In one instance a patient with intractable hemoptysis was sufficiently improved to return to part time occupation.

Summary and Conclusion

1. Surgical removal of a primary carcinoma of the lung along with the draining lymph nodes still remains the treatment of choice in operable neoplasms of the lung. Experiences of the authors would indicate that further exploration of the advantages of a combined adjuvant program of pre- and postoperative chemotherapy along with radical surgical excision of the primary carcinoma of the lung might be most rewarding in those instances where undifferentiated carcinoma can be demonstrated preoperatively. It is in this particular category that the poorest results and lowest survival rates have been experienced in the past.

2. Chemotherapy offers a most welcome and effective tool in the management of inoperable primary carcinoma of the lung. Many of the patients in the present series have been improved uniformly following chemotherapy. The general improvement in the patients' well-being usually accompanies reduction in toxemia, return of the appetite and gain in body weight.

3. Chemotherapy has produced very gratifying results according to the criteria for estimating improvement, in patients with metastatic breast carcinoma involving the lung or pleura with or without pleural effusion.

Figure 3A: Metastatic breast carcinoma to right lung and pleura. Figure 3B: Same patient 13 days after chemotherapy. Patient alive and well two years and four months after treatment.
4. Determination of the effectiveness on the increase in survival rate in those instances in which chemotherapy is used as an adjuvant agent in the association with elective surgical removal of a carcinoma of the lung should be explored in the future.

**Resumen**

1. La excisión del carcinoma primario del pulmón así como la exclusión de los ganglios de drenaje es aún el tratamiento de elección en las neoplasias operables del pulmón. Las experiencias de los autores indicarían que sería fructífera una investigación más adelante sobre las ventajas de un plan de quimioterapia preparatoria y postoperatoria en el carcinoma pulmonar resecado, en aquellos casos en que se puede demostrar antes de la operación el carácter no diferenciado del tumor. Es en este grupo de neoplasmas que se han observado en el pasado los resultados menos satisfactorios.

2. La quimioterapia ofrece un instrumento bienvenido y efectivo en el tratamiento del carcinoma inoperable del pulmón. Muchos de los enfermos en las series presentes han mejorado de modo uniforme después de la quimioterapia. La mejoría general y el bienestar en los enfermos se acompaña de reducción de la toxemia, vuelta del apetito y aumento de peso.

3. La quimioterapia ha producido satisfactorios resultados de acuerdo con el criterio para estimar la mejoría en enfermos de carcinoma mamario metastásico que ha invadido el pulmón, con o sin derrame pleural.

4. La determinación de la efectividad por el aumento de la media de sobrevida en los casos en que se ha usado la quimioterapia como adyuvante de la extirpación quirúrgica debe explorarse en el futuro.

**Zusammenfassung**

1. Die chirurgische Entfernung eines primären Lungencarzinoms zusammen mit den regionären Lymphknoten bleibt noch immer die Behandlung der Wahl bei operablen Neoplasmen der Lunge. Die Erfahrungen der Verfasser deuten darauf hin, daß sich weitere Untersuchungen hinsichtlich der Vorteile einer kombinierten zusätzlichen Program-

**References**


