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Neoadjuvant Therapy of Lung Cancer*

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(Chest 1991; 100:845-46)

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n patients who have locally advanced stage IIIA disease and multistation N2 disease, resection is unlikely to be complete even when radical mediastinal node dissection is employed. Patients with incomplete resections have a minimal chance of 5-year survival.1 There has been recent interest in the addition of postoperative therapy for patients with incompletely resected disease. The National Institutes of Health Lung Cancer Study Group (LCSG)8 has reported a minimal increase in survival with the addition of cyclophosphamide, Adriamycin (doxorubicin hydrochloride), and cisplatin (CAP) chemotherapy to irradiation compared to postoperative irradiation alone. The survival benefit was not clearly significant. Postoperative irradiation has been shown to reduce the incidence of local recurrence but does not provide any survival benefit.5

The use of preoperative, or "neoadjuvant," therapy has become popular in recent years. It is theoretically possible that chemotherapy may be of more benefit if given preoperatively. Of more practical value, however, is the demonstration of response to the specific chemotherapy regimen prior to resection when such a measure of response can be made. If response is observed, then administration of the same regimen postoperatively seems a more reasonable proposition. Neoadjuvant therapy might possibly reduce the size of the primary tumor and nodal metastasis, thereby enabling surgical resection, and at the same time deal with distant micrometastases when they are still of minimal size. This treatment plan has been studied extensively in other malignancies, such as osteogenic sarcoma,4 esophageal cancer,5 and cancer of the bladder, rectum, and anus. There have been a number of retrospective and phase II preliminary studies of neoadjuvant therapy in bronchogenic carcinoma. An excellent recent report by Einhorn7 reviews the subject in detail.

The LCGS has completed a pilot study in patients with technically unresectable N2 disease. These patients received CAP plus fractionated radiation (3,000 cGy in 10 fractions). Forty-two patients were studied, of whom 39 were eligible. Only 13 of these patients went on to complete resection.5 A subsequent LCGS trial in the same group of patients studied preoperative chemotherapy with 2 cycles of cisplatin and continuous infusion of 5-fluorouracil plus radiation (3,000 cGy in 15 fractions). Sixty-two patients began therapy, and 56 were able to complete the prescribed course. Three complete responses were observed and 35 partial responses. All complete responders had resectable disease, and 27 of the partial responders were completely resected. Nonetheless, only 3 of 62 patients had a complete response to induction chemotherapy.

It appears that induction chemotherapy with mitomycin, vinblastine, and platinum (MVP) without radiation will

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provide a higher incidence of complete response. The Eastern Cooperative Oncology Group reported a response rate of over 50% in patients with locally advanced non-small cell lung cancer. A more intensive MVP regimen in patients with ipsilateral N2 disease provided an 18% complete response rate and a 58% clinical partial response. Four of 7 patients with a complete clinical response were found on pathologic examination to have a complete pathologic response as well. The response rate for adenocarcinoma was 50%, for squamous carcinoma 77%, and for large cell carcinoma 73%. The same group has reported a pilot trial of preoperative chemotherapy with MVP. Fifty-eight patients were treated with a response rate of 74%. Forty-two patients underwent thoracotomy, and 33 underwent complete resection. Nine patients had no pathologic evidence of tumor in the resected specimen. Unfortunately, this study is weakened by the absence of accurate preoperative surgical staging by mediastinoscopy. The Toronto group has now completed a pilot study using the same high-dose-platinum MVP regimen and has achieved similarly encouraging results.

The role of radiotherapy in the preoperative management of these patients is not clear. Large prospective randomized studies of preoperative radiotherapy dealt for the most part with patients who were initially presumed to have operable disease. The rate of resectability was increased, but no survival benefit was observed. A National Cancer Institute collaborative study included patients who were presumed operable. Of 452 patients who entered the study, 152 were considered to have resectable disease following preoperative administration of 4,000 cGy of radiation. These patients were then randomized to resection or observation. There was no survival difference in the groups. There were, however, major complications in the surgical group. Unfortunately, this study is deficient for lack of stratification by TNM stage, performance status, or histologic features. The radiation was not up to current technologic standards, and the total dose was low (4,000 cGy in 4 weeks). A number of nonrandomized studies of preoperative radiation have been published but are difficult to assess in view of differences in patient population, preoperative staging, and surgical judgment. Nonetheless, it appears that state-of-the-art radiation in these patients with bulky N2 disease provides a survival benefit which equals that of surgery alone.

The notion of neoadjuvant therapy in patients with bronchogenic carcinoma is dependent upon the assumption that the chemotherapy is effective. It is probable that response rates for stage III disease exceed those reported for stage IV disease. Nonetheless, an effective regimen with an impact on survival has not yet been identified. The myriad of retrospective reviews and phase II trials do give some information with respect to response rates but are of no value in determining survival benefit. Fortunately, the LCSG is embarking on a prospective randomized trial to compare preoperative MVP chemotherapy with preoperative irradiation (4,400 cGy in 22 fractions) in patients with locally advanced stage IIIA (bulky N2) disease or selected stage IIIB (T4) disease. It is unfortunate, however, that the combination of neoadjuvant therapy and surgery is not being compared with radiation alone, which until very recently has been considered standard therapy in these patients.

At the present time, there are no prospective randomized data that support the use of neoadjuvant chemotherapy in patients with locally advanced bronchogenic carcinoma. Application of these regimens to patient care should be restricted to study protocols at the present time.

REFERENCES