Preoperative Neoadjuvant Therapy in Non–Small-Cell Lung Cancer: Open Season?

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Neoadjuvant therapy refers to chemotherapy or radiation administered before surgery when surgery is intended as the definitive local/regional treatment (1). The objectives of neoadjuvant therapy are to enable the resection of an otherwise unresectable neoplasm, to reduce the risk of local or of distant recurrences, and to increase the survival rate. A review of the recent literature indicates that well over 500 patients with Stage IIIA lung cancer have been treated with neoadjuvant therapy (2). In addition to these patients, an untold number of patients throughout the country have been treated “off protocol” (ie, not as part of an organized clinical trial), a fact which reflects the enthusiasm for this treatment, not only among university-based oncologists but also among community-based oncologists.

However, it is difficult to interpret the data because patients in these various studies are not comparable. Preoperative staging procedures have not been consistent. Some of the criteria have included disease localized to the thorax but deemed unresectable. Others have included patients with either stage IIIA or IIIB disease. In addition, all these trials have been phase II trials. Drawing conclusions regarding survival from phase II trials is very hazardous, since one cannot control for the impact of factors other than the effect of therapy, such as weight loss, performance status, and physician selection — any or all of which may be responsible for seemingly improved survival.

Nevertheless, the data from these phase II studies are most provocative. The clinical response rates to the neoadjuvant therapy of 50% to 70% and the histologic complete response rate of 20% have led many to assume that neoadjuvant therapy will result in improved survival. This assumption may or may not be true. It is apparently not true in the cases of head and neck cancer (3,4) and esophageal cancer (5). Therefore, one cannot automatically assume that clinical and histologic responses to neoadjuvant therapy will translate into improved survival.

Unfortunately, patients are told that surgery is the only curative modality in lung cancer. The statement is true as it relates to patients with T1N0 and T2N1 disease, to certain patients with T3N0 disease, and to a very small subset of patients with N2 disease. However, patients with more advanced lung cancer confined to the thorax are often told to “have surgery in case it might help you — it’s your only chance.” This advice hardly seems justified by the evidence. Perhaps neoadjuvant therapy is popular because it involves physicians from all of the treatment modalities.

Placing these considerations aside, does the experience with the more than 500 patients who have received neoadjuvant therapy support the conclusion that surgery improves their cure rate or quality of life? There is one fact that is crystal clear: surgery in lung cancer is almost never palliative. Also, with the current state of the art, subtotal resection or “debulking” is never indicated. Is it logical to assume, based on experience with other tumors, that surgery actually improves the cure rate for patients receiving neoadjuvant therapy compared with that for patients receiving either chemotherapy or radiation therapy alone (or a combination of the two) but no surgery? Certainly, the response rates of 60% to 70% are promising. However, the median duration of survival for the resected patients in all of these phase II studies ranges from 16 to 25 months. This survival period is not much different from that experienced by historical controls treated with combined radiation therapy and chemotherapy but without surgery (6).

Is there a subset of patients who may benefit from neoadjuvant therapy? While the paper by Weiden and Piantadosi (1) in this issue of the Journal does not document an increased duration of survival for patients with histologic complete responses, other investigators have reported improved survival in these patients (2). It must be emphasized that in phase II trials survival analyses are subject to considerable bias (due to variability of patients included and treatments employed) and are simply not reliable. What is clear from these phase II trials is that neoadjuvant therapy does alter patterns of recurrence. Local recurrences are dramatically diminished in these patients; however, systemic recurrences, especially brain recurrences, greatly offset this benefit.

Therefore, the data and even the logic cannot lead one to assume that surgery adds any benefit to chemotherapy and/or radiation therapy in otherwise surgically incurable patients. In order to answer these questions, prospective randomized phase III trials must be done. The Southwest Oncology Group is attempting to obtain funding for a randomized study comparing (a) neoadjuvant etoposide and cisplatin combined with radiotherapy, followed by surgery and additional chemotherapy, to (b) radiation therapy alone. Such phase III randomized trials will clearly address the issue of the role of surgery in patients who have responded to neoadjuvant therapy. Unfortunately, there are few NCI funds targeted for non–small-cell lung cancer neoadjuvant trials, and, therefore, it is unlikely that such trials will move forward at an acceptable pace. It is a great pity that the number one cancer killer in men and women in the United States is allocated so few resources at the federal level.

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Expression of the nm23 Gene and Breast Cancer Prognosis

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Carcinoma of the breast is the most common malignancy in women in the United States, and is second only to lung cancer as a cause of cancer-related death in women (1). It has been estimated that 1.5 million women will be diagnosed with breast cancer in the 1990s, and of these 30% will succumb to the disease.

The modalities for the treatment of this disease as well as the aggressiveness of the treatment plan are variable and the decision as to which approach to take can frequently depend on information regarding the nature of the biologic behavior of an individual tumor. As a result, a number of prognostic indicators have been examined for their ability to predict the behavior of a given tumor. The most generally accepted, and to date, best prognostic indicator in the management of breast cancer is the presence or absence of malignant cells in the axillary lymph nodes (2). Patients with involved lymph nodes are known to be at high risk for recurrence and to have a shortened survival; the greater the number of involved nodes, the greater the risk. There is little debate that these patients should receive adjuvant chemotherapy and/or endocrine therapy. A significant number of women diagnosed in 1990, however, had node-negative breast cancer. While these patients as a group have a more favorable overall prognosis than patients with node-positive disease, it is known that between 20% and 30% will experience a recurrence. Given these statistics and the difficulty of effectively treating recurrent disease with curative results, many oncologists have advocated the use of adjuvant therapy in node-negative patients with the intent of benefiting those who might otherwise have a recurrence. Data from several large clinical trials indicate that such a therapeutic approach decreases disease-free recurrence rates in these patients (3-6), and as a result, many believe that adjuvant therapy will improve overall survival in this group of women. In fact, this concept has led the NCI to issue a clinical alert asking physicians to consider the use of this treatment modality in node-negative patients (7).

Counter-arguments to the use of adjuvant therapy in all node-negative patients, however, are the short-term and potentially long-term risks of such treatment. Should the 70% to 80% of node-negative patients who will not experience a recurrence be put at risk to benefit those who will? One of the major objectives in breast cancer research over the past decade has been to identify additional prognostic factors that will distinguish those patients more likely to have recurrent and/or aggressive disease.

To this end, a variety of potential prognostic factors have been investigated, including tumor size (8,9), histologic and nuclear grades (10), hormone receptor status (11,12), proliferative rate and ploidy (13-15), growth-factor receptors such as the protein products of the HER-2/neu (also known as the ERBB2) and the epidermal growth-factor receptor (EGFR) genes (16-19), and cathepsin D production (20). While a substantial research database exists for some of these factors, only those node-negative patients with tumors less than 1 cm in size, who are expected to experience recurrences at a rate of less than 10% over a period of 10 years, have been advised against systemic therapy by the most recent NIH Consensus Development Conference (21).

Several reasons exist for the lack of significant progress in first identifying and then implementing the use of new and effective prognostic indicators. Examples of these problems are apparent in the research conducted in several laboratories, including our own, on the utility of the HER-2/neu gene for predicting outcome in human breast cancer. Disagreement concerning what constitutes and how best to measure a significant genetic alteration such as amplification is one such problem (22). Second, both the techniques and the reagents used to measure HER-2/neu expression have been quite variable from therapy with 120-hour 5-FU infusion and cisplatin. Cancer 55:1123-1128, 1985

References


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