Chemotherapy in Early Stage Non Small Cell Lung Cancer

Lung cancer is one of the most common cancers, and is the leading cause of cancer death in the U.S. and internationally. Worldwide, there are an estimated 1.61 million new cases (estimated 228,190 in the U.S. in 2013) and over 1.38 million deaths (estimated 159,480 in the U.S. in 2013) each year. This is compared to 600,000 cases diagnosed in 1975, and the increase is directly related to tobacco use.
Research into screening tests is aimed at identifying patients with earlier stage disease. Yet, even when diagnosed early, the percentage of patients alive in five years ranges from only 30-60%. The five-year survival rate for all stages combined is a mere 15%. Lung cancer is further divided into two categories, small cell lung cancer and non-small cell lung cancer, which are treated differently. Non-small cell lung cancer makes up about 87% of cases, and is the type which we will discuss in this article.

When possible, early stage lung cancer is treated with surgery to resect the tumor. (See staging of lung cancer) When a recurrence occurs, it is 2-3 times more likely to be somewhere else in the body, as opposed to the lung. This brings up the question: would chemotherapy after surgery (also called adjuvant chemotherapy) have killed those cancer cells that were able to survive the surgery and later reappear somewhere else in the body? This question has puzzled doctors for some time. Chemotherapy is not without side effects, and one would not want to undergo chemotherapy unless one could achieve some gain in survival. There are several studies which have looked at this question in early stage disease, so let's review them.
Early studies did not have large numbers of participants, which makes it difficult to interpret those results. Researchers can combine the results of multiple studies to get a bigger perspective; this is called a meta-analysis. In 1995, researchers performed a meta-analysis of all the studies of early-stage non-small cell lung cancer from 1965 to 1991. They found that chemotherapy with radiation actually reduced survival in these studies, but the types of chemotherapy drugs used varied widely, making it difficult to apply this finding to the current chemotherapies. They did find that chemotherapy regimens using cisplatin, even without radiation, increased the five-year survival by 5%. This number was not "statistically significant", meaning that this increase could have been just luck. A statistically significant result is one that is more than likely true, and not likely to happen by chance. Doctors use statistical significance as a measure of a therapy's success. Although the 5% difference was not statistically significant, it raised interest in doing further studies with early stage patients.

The next study was called Adjuvant Lung Project Italy (ALPI), and included 1,088 patients with stage I, II & IIIA disease. It showed no benefit in survival by adding cisplatin-based chemotherapy (meaning a regimen of medications that includes cisplatin and usually not more than 3 chemo drugs). One year later, results from the International Adjuvant Lung Cancer Trial (IALT) were released. The study included 1,867 patients, stages I, II & IIIA, who were treated with cisplatin-based chemotherapy. Results showed a 4% improvement in overall survival at five years. The overall survival represents the number of patients who were alive at five years, but some of these patients may have had active lung cancer. (In contrast, disease-free survival only counts those patients who were alive AND free of disease at that time point.) This 4% improvement includes all studied stages of disease, so the number could be less impressive if you were only looking at stage IB disease, but that was not done in this study. The next three studies did break down the results by stage, helping to answer some of the questions raised by IALT.

A trial conducted by The National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) included 482 generally healthy patients with stage IB or II surgically resectable lung tumors. Patients were assigned to receive either chemotherapy with cisplatin and vinorelbine or observation. The five-year overall survival was 15% higher in the chemotherapy group (69% survival with chemo vs. 54% survival with observation). These numbers include stage IB and II disease. When researchers separated out stage IB, they found no "statistically

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significant" benefit for the chemotherapy group with stage IB.
The next study, run by the Cancer and Leukemia Group B (CALGB), included 344 patients with stage IB resectable disease. Patients were assigned to receive either chemotherapy with paclitaxel and carboplatin or observation. This study was first reported in 2004, with a follow up of 34 months. The study had been stopped early because an analysis showed a statistically significant benefit in the chemotherapy arm. The four-year overall survival was 12% higher in the chemotherapy group (71% survival with chemo vs. 59% survival with observation) at the time of the original report. The group also saw improvement in the mortality caused by lung cancer, with 19 deaths in the chemotherapy group and 34 deaths in the observation group attributed to lung cancer. There were no deaths related to chemotherapy toxicity, and neutropenia was the most common toxicity.

At the 2006 national meeting (ASCO), the anxiously awaited updated results of this study were presented. This report had a follow up of 54 months, and at that point, the overall survival between the two groups was no longer statistically significant [63% in chemotherapy arm vs. 57.3% in the observation arm ($p=0.10$)]. At first glance, it would seem that chemotherapy is of no advantage to stage IB patients, but there is more to be considered. Given that this trial was closed early, the number of patients is smaller, and it is hard to tell if a larger sample size would have shown more benefit. The investigators plan to update this trial as time goes on, but this leaves current patients and oncologists with a difficult decision. Of note, the investigators found through an unplanned subset analysis that patients with tumors greater than 4cm in size derived more benefit from chemotherapy. One must be very cautious in making decisions on subset analyses because the trial was not actually designed to answer this question. Subset analyses should be considered hypothesis generating and not definitive. Thus this should be considered a negative study for the use of chemotherapy in patients with IB NSCLC.
The last study, called The Adjuvant Navelbine International Trialist Association (ANITA), assigned 840 patients with resected IB, II, or IIIA disease to receive either chemotherapy with vinorelbine and cisplatin or observation. This study found improved overall survival in the chemotherapy group, with 51% survival with chemo vs. 43% survival with observation. This study, like the NCIC-CTG study, did not find a statistically significant benefit for stage IB patients. All three of these studies reported that the chemotherapy regimens were well tolerated by patients, with acceptable side effect profiles.
Based on the previous three trials, oncologists must discuss the pros and cons of adjuvant chemotherapy with each patient on an individual basis. What does remain clear is that patients with Stage IA disease do not seem to derive any benefit from adjuvant treatment with currently available chemotherapy regimens. Although some will argue in favor of chemotherapy for certain subsets of IB NSCLC, there is no definitive prospective evidence that patients derive benefit from chemotherapy. Ultimately, patients must discuss the pros and cons of their individual situation with their oncologist.

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