Patient Subsets Benefiting from Adjuvant Therapy Following Surgical Resection of Non–Small Cell Lung Cancer

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Abstract

Adjuvant chemotherapy is the standard of therapy for some patients with stages I, II, and III breast and colon cancer. The therapeutic efficacy of adjuvant chemotherapy following surgical resection of early stage non–small cell lung cancer (NSCLC) has been less clear. A meta-analysis was reported in 1995 of patients who underwent surgical resection for early stage NSCLC and were then randomized to either observation or chemotherapy. This meta-analysis showed a 13% reduction in the hazard ratio of death, leading to a 5% absolute improvement in survival 5 years after the start of adjuvant cisplatin-based chemotherapy treatment compared with observation only. Multiple prospective randomized trials for patients with NSCLC were planned and undertaken to attempt to validate the observations of the meta-analysis. Six trials with ≥150 patients with early stage NSCLC (stages I–IIIA) on each arm have been reported in the last 2 years. Four of the six trials show a survival advantage for the patients with early stage NSCLC treated with adjuvant chemotherapy compared with those who underwent observation. The survival benefit in these four studies varies from a 4% to a 16% survival advantage at 4 to 5 years after the start of chemotherapy. The hazard ratio of death for the patients treated with chemotherapy ranged from 0.61 to 0.86 compared with patients on observation. Thus, the information available at the current time supports the administration of chemotherapy for patients with stages IB and II NSCLC. Further research will be needed to define the role of adjuvant chemotherapy and its use in conjunction with chest radiotherapy for the treatment of patients with resected stages IA and IIA NSCLC.

The most effective treatment for early stage (I–IIIA) non–small cell lung cancer (NSCLC) is surgical resection. Despite surgical resection, 50% to 60% of patients with stages I to IIA NSCLC relapse and die from their lung cancer (1, 2). There have been attempts to reduce the risk of relapse and death from lung cancer by giving adjuvant chemotherapy to patients following surgical resection (3). This approach has been successful in patients with breast and colon cancer where some patients with stages I to III cancer are routinely given adjuvant hormonal therapy (breast cancer), chemotherapy, or both.

Small randomized trials for patients with early stage NSCLC done over the last 30 years have been jointly analyzed in a meta-analysis reported in 1995 (3). This analysis showed a 5% survival advantage at 5 years for patients with surgically resected early stage NSCLC treated with cisplatin-based chemotherapy compared with those on observation alone. This led to the planning and execution of multiple national and international trials that were adequately powered to look for this small benefit of an absolute increase of 5% at 5 years. The results of these trials have been reported in the last 2 years. The trials that are reviewed here are those that entered ≥150 patients with surgically resected stages I to IIA NSCLC per arm. These trials are discussed in the order in which they have appeared in the literature or were presented at international meetings. The six trials have used different types of chemotherapy, included different proportions of stages IA to IIA NSCLC, and have different methods of reporting their results. The purpose of this article is to determine if there are consistent effects of adjuvant treatment by the type of chemotherapeutic agent, stage, gender, or ability to administer the agents.

Patients and Methods

Mitomycin, vindesine, and cisplatin adjuvant trial for patients with resected stages I to IIA non–small cell lung cancer. This trial is called Adjuvant Lung Project Italy (ALPI; ref. 2). Patients with stages I to IIA NSCLC who successfully underwent a complete resection of their tumor, including mediastinal lymph nodes, were eligible for this trial. The patients were randomized to treatment with 8 mg/m² mitomycin on day 1, 3 mg/m² vindesine on days 1 and 8, and 100 mg/m² cisplatin on day 1 of a 3-week cycle or to observation. Adverse effects were monitored during the 21-day cycles, and dose adjustments were made based on the toxicities encountered. If tolerated, chemotherapy was given for three cycles. At each institution, investigators decided whether or not to administer chest radiotherapy after the completion of chemotherapy according to their institutional policy.

Cisplatin-based adjuvant trial for patients with resected stages I to IIA non–small cell lung cancer. This trial is called International Adjuvant Lung Cancer Trial (IALT; ref. 1). Patients with stages I to IIA NSCLC who successfully underwent a complete resection of their tumor were eligible for this trial. The patients were treated with 80 to 120 mg/m² of
cisplatin given for three to four cycles of treatment in combination with etoposide, vinblastine, vinorelbine, or vindesine, or were managed by observation only. Adverse effects were monitored during the 21- to 28-day cycles, and dose adjustments were made based on the toxicities encountered. The treatment was administered for three to four cycles if the patients tolerated the chemotherapy. Investigators from each institution had the option of administering chest radiotherapy after the completion of surgery plus chemotherapy for patients with N1 or N2 disease according to their institutional policy.

Uracil-tegafur adjuvant trial for patients with resected stage I adenocarcinoma of the lung. This trial is called the UFT trial (4). Patients between the ages of 45 and 75 years who underwent successful resection of their stages IA and IB adenocarcinoma of the lung were eligible for this trial. The patients were randomized to be treated with the uracil-tegafur combination at a dose of 250 mg/m² tegafur (as capsules containing 100 mg of tegafur and 224 mg of uracil) given orally each day for 2 years or observation. Adverse effects were monitored every 3 months during the treatment and dose adjustments were made based on the toxicities encountered. There was no chest radiotherapy administered to the patients.

Cisplatin-based adjuvant trial for patients with potentially resectable non–small cell lung cancer. This study is called the BIG Lung Trial (5). Patients with NSCLC deemed potentially resectable, or who had undergone resection, were eligible for the trial. The patients could be treated before or after surgical resection with 50 to 80 mg/m² cisplatin administered every 3 weeks for three cycles of treatment combined with one of four regimens (mitomycin and ifosfamide, mitomycin and vinblastine, vindesine, or vinorelbine) or observation. The chemotherapy was administered either before or after surgery and chest radiotherapy at the discretion of the investigators. Adverse effects were monitored during the 21- to 28-day cycles, and dose adjustments were made based on the toxicities encountered.

Vinorelbine cisplatin adjuvant trial for patients with resected stages IB and II non–small cell lung cancer. This trial is referred to by its cooperative group name, JBR.10 (6). Patients with stages IB to II NSCLC who successfully underwent a complete resection of their tumor were eligible for this trial. The patients were randomized to be treated with 25 mg/m² vinorelbine weekly and 50 mg/m² cisplatin on days 1 and 8 of a 4-week cycle or to observation. Adverse effects were monitored during the 28-day cycles, and dose adjustments were made based on the toxicities encountered. Treatment was administered for four cycles if the patients tolerated the chemotherapy. There was no planned chest radiotherapy administered to the patients.

Paclitaxel carboplatin adjuvant trial for patients with resected stage IB non–small cell lung cancer. This trial is referred to by its cooperative group name, CALGB 9633 (7). Patients with stage IB NSCLC who successfully underwent a complete resection were eligible for this trial. The patients were randomized to be treated with paclitaxel, 200 mg/m², and carboplatin with an area under the curve of 6 mg/mL/min over 3 weeks or to observation. Adverse effects were monitored during the 21-day cycles, and dose adjustments were made based on the toxicities encountered. The treatment was administered for four cycles if the patients tolerated the chemotherapy. There was no planned chest radiotherapy administered to the patients.

Results

Trial design and patient characteristics in the adjuvant chemotherapy trials following surgical resection of non–small cell lung cancer. The six trials reported here all started patient accrual in 1994 to 1996, shortly after the results of the meta-analysis became available (Table 1). They completed patient accrual by 1997 to 2003. The Japanese UFT trial was able to accrue 979 patients limited to those with stages IA and IB adenocarcinoma of the lung in just 3 years. The three European studies were able to complete their accrual of patients with stages I to IIIA in 5 years (ALPI and IALT trials) or 6 years (BIG trial). The studies that took the longest to accrue (7 years) were done in the United States and Canada and focused on just stage IB or IB plus II in populations that were 64% or 65% male (CALGB 9633 and JBR.10, respectively). The European trials had a predominance of men (86%, 80%, and 69% for the ALPI, IALT, and BIG, respectively), whereas the Japanese trial focused on early stage adenocarcinoma (stages IA and IB) and had a majority of women (51%). The median ages were similar in all six trials, ranging from 59 to 62 years. The Japanese UFT Trial restricted their participants to ages 45 to 75 years, so their age range was more limited than the European and North American trials.

Treatment of the patients participating in the adjuvant chemotherapy trials. The frequency of more extensive surgery (pneumonectomy) was reported in five of the trials and varied with differing clinical practice and the disease stages of the patients participating in the trials (Table 1). The percentage of patients treated with pneumonectomy was higher in two of the European (25% for ALPI and 35% for IALT) and the Canadian (24% for JBR.10) trials than in the Japanese (<1%) and U.S. (11% for CALGB 9633) trials. The three European trials allowed chest radiotherapy either after the adjuvant chemotherapy or after surgery for those patients randomized to the no chemotherapy arm (see Table 1). In ALPI, 65% of the patients treated with chemotherapy and assigned to chest radiotherapy completed their course of treatment compared with 82% who underwent observation. In IALT, 70% of the patients treated with chemotherapy and assigned to chest radiotherapy completed their course of treatment compared with 84% who did not get chemotherapy. In the BIG lung cancer trial, 52 patients (14% of the total) underwent chest radiotherapy. The other three trials with earlier stage patients (stages IA-II) did not explicitly report on the administration of chest radiotherapy.

Most of the patients completed their planned courses of chemotherapy, and deaths related to chemotherapy treatment were rare. In the chemotherapy arm of the ALPI trial, 69% of patients received the planned three courses of mitomycin, vindesine, and cisplatin. There were 10 treatment-related deaths reported in the ALPI trial, 3 in the mitomycin, vindesine, and cisplatin arm and 7 in the observation arm (<1% total). In the IALT trial, 74% of patients in the chemotherapy arm received at least three courses of their planned cisplatin-based therapy. In this trial, there were seven deaths related to complications of chemotherapy administration (<1%). The patients in the Japanese UFT trial were compliant with their regimen 74% of the time at 1 year and 61% at 2 years. There were no treatment-related deaths reported in the UFT trial. In the BIG trial, 64% of patients received their three planned cycles of cisplatin-based therapy. There were six treatment-related deaths in the chemotherapy arm of this trial (3%). Altogether, 65% of the patients in the chemotherapy arm of the JBR.10 trial completed at least three of their planned four courses of vinorelbine and cisplatin. There were two treatment-related deaths in the chemotherapy arm of the JBR.10 trial (<1%). Finally, 85% of patients in the CALGB 9633 trial received their planned four courses of paclitaxel and carboplatin. There were no treatment-related deaths reported in the CALGB 9633.

Efficacy of the treatment for the patients participating in the adjuvant chemotherapy trials. Four of the six trials reported a
reduction in the hazard ratio of death and survival advantage at 4 to 5 years for the patients treated with adjuvant chemotherapy compared with those on observation (Table 2). Five of the six trials used platinum-based chemotherapy similar to the regimen found to confer a survival benefit in the meta-analysis, whereas the sixth used tegafur and uracil (UFT). Three of these five trials using platinum-based chemotherapy (IALT, JBR.10, and CALGB 9633) and the trial using UFT showed a survival benefit for the treated patients compared with those on the observation arm. It is difficult to compare the relative efficacy of the different chemotherapy regimens across the arms of the trials, and we await the future results of trials comparing different types of chemotherapy. The magnitude of the benefit for the European trials was small. There was no difference overall between the patients on the ALPI and BIG trials treated with resection plus chemotherapy versus those treated with surgery and observation. The reduction in the hazard ratio of death in the IALT trial (0.86; 95% confidence interval, 0.76-0.98) was nearly identical to the reduction in the hazard ratio of death in the meta-analysis (0.87) compared with patients undergoing observation. This translated into a 4.1% absolute increase in the proportion of patients alive after 5 years (44.5% for those treated with adjuvant chemotherapy versus 40.4% for those on the observation arm), comparable with the 5% benefit seen in the meta-analysis (3). The reduction in hazard ratios of death for the chemotherapy-treated patients was remarkably similar in the other three trials. The hazard ratio of the patients treated with chemotherapy on the Japanese trial was 0.71; the JBR.21 trial was 0.7 (P = 0.012); and CALGB was 0.62. This translated into a 3% to 15% absolute increase in the proportion of patients alive after 4 to 5 years for those treated with adjuvant chemotherapy compared with those on the observation arm.

Discussion

These six trials provide information about the subsets of patients with NSCLC who benefit from adjuvant chemotherapy following surgical resection. Most information is by disease

| Table 2. Demographics and treatment variables of patients with resected NSCLC participating in the adjuvant chemotherapy trials |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| ALPI            | IALT            | UFT             | BIG             | JBR.10          | CALGB 9633      |
| No. patients    | 1,088           | 1,867           | 979             | 381             | 482             | 344             |
| Gender          | Male (86%)      | Female (14%)    | Male (61%)      | Female (39%)    | Male (51%)      | Female (49%)    |
| Male            | 937             | 1,502           | 477             | 261             | 313             | 220             |
| Female          | 151             | 366             | 502             | 120             | 169             | 124             |
| Stages          |                |                 |                 |                 |                 |                 |
| I               | 423 (39%)       | 681 (36%)       | IA—716 (73%)    | IB—263 (27%)    | IB—219 (45%)    | IB—344 (100%)   |
| II              | 355 (33%)       | 452 (24%)       | 145 (38%)       | 263 (55%)       |                 |                 |
| IIIA            | 310 (28%)       | 734 (39%)       | 133 (35%)       |                 |                 |                 |
| Pneumonectomy   | 274 (25%)       | 648 (35%)       | 2 (<1%)         | Not reported    | 116 (24%)       | 38 (11%)        |
| Chest radiotherapy | 470 (43%) | 572 (31%)   | 52 (14%)        |                 |                 |                 |

| Table 2. Hazard ratios of death and survival benefit at 2 to 5 years by subsets for patients with NSCLC treated with chemotherapy compared with patients undergoing observation |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| ALPI            | IALT            | UFT             | BIG             | JBR.10          | CALGB 9633      |
| No. patients    | 1,088           | 1,867           | 979             | 381             | 482             | 344             |
| Hazard ratio for entire cohort | 0.96 (0.81-1.13) | 0.86 (0.76-0.98) | 0.71 (0.52-0.98) | 1.02 (0.77-1.35) | 0.60            | 0.62 (0.42-0.95) |
| Survival advantage for adjuvant therapy/control for entire cohort | Increase of 1% at 5 y (confidence interval of 4%-7%) | Increase of 4.1% at 5 y (confidence interval of 44.5%-40.4%) | Increase of 3% at 5 y (confidence interval of 88%-85%) | Decrease of 2% at 5 y (confidence interval of 60%-58%) | Increase of 15% at 5 y (confidence interval of 54%-60%) | Increase of 13% at 4 y (confidence interval of 59%-71%) |
| Gender          | Not given       | No difference   | No difference   | No difference   | No difference   | No reported     |
| Stages          |                |                 |                 |                 |                 |                 |
| I               | 0.97 (0.71-1.33)| No difference   | IA—0.97 (0.64-1.46) | IB—0.48 (0.29-0.81) |                 |                 |
| II              | 0.80 (0.60-1.06)| No difference   | IB—0.48 (0.29-0.81) |                 |                 |                 |
| IIIA            | 1.06 (0.82-1.38)| No difference   | IB—0.48 (0.29-0.81) |                 |                 |                 |
stage, but there is also some information on the benefit of adjuvant chemotherapy treatment by gender, age, histology, and type of chemotherapy, and on the impact of chest radiotherapy.

The most consistent benefit from adjuvant chemotherapy was observed in patients with resected stages IB to II NSCLC. All three of the trials that prospectively studied the patients with stages IB to II disease observed a benefit for these patients (UFT, JBR.10, and CALGB 9633). The patients in these three trials were treated with chemotherapy alone because chest radiotherapy was not included in the therapeutic regimen. The magnitude of the benefit showed a reduction in the hazard ratio of death to 0.48 to 0.70 for those treated with chemotherapy compared with those on observation. The subset analysis by stage of the ALPI trial showed patients with stage II had a reduction in the hazard ratio of death to 0.80 (95% confidence interval, 0.6-1.06), whereas the hazard ratio for stages I and III were 0.97 and 1.06, respectively. The subset analysis by stage of the IALT trial showed patients with stage III had the greatest reduction in the hazard ratio of death compared with stages I and II. The subset analysis of the BIG trial showed no evidence of a survival benefit for any stage of patients treated with chemotherapy compared with those undergoing observation. The BIG trial had only 381 patients, was based on clinical staging, and allowed investigators to administer the chemotherapy both before and after surgical resection. The study was underpowered so it was unable to detect a 5% difference in outcome at 5 years and its ability to provide information by subsets was very limited.

It seems clear from the information provided by these six trials that patients with surgically resected stages IB to II NSCLC should be treated with postoperative chemotherapy as given in the trials. It remains a challenge to determine the appropriate postoperative treatment for patients with resected stage IIIA NSCLC. In addition to the studies reported here, a prominent study looked at the effects of adding etoposide and cisplatin to chest radiation therapy for 488 patients with resected stages II and IIIA NSCLC (8). These patients did not benefit from the addition of chemotherapy. The clinical research to define the roles of chemotherapy and chest radiotherapy following resection of patients with stage III NSCLC has not yet provided a clear plan for their effective management.

There are two studies that show a therapeutic advantage and provide information about the benefit by gender, age, and histology. The JRB.10 and CALGB 9633 have only been reported at international meetings and the information by subsets is not yet available. The IALT and UFT studies show a benefit for both men and women, with no consistent impact by age. For patients on the IALT trial, the benefit was similar for both squamous cell and adenocarcinoma of the lung. The UFT trial enrolled only subjects with adenocarcinoma.

The information available now shows a consistent benefit for giving adjuvant chemotherapy to patients with surgically resected stages IB to II NSCLC, if the mature results of JBR.10 and CALGB 9633 provide information consistent with the initial reports. It seems that gender, age, and histology do not have a major impact and there is no information to suggest that these factors should be used to select patients. The management of patients with resected stage III NSCLC remains unclear, and further research is needed to define the appropriate roles of chest radiotherapy and chemotherapy in this patient group.

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### Open Discussion

**Dr. Thomas Lynch:** Dr. Henschke, what do you think is a reasonable scheme for following up cured or resected lung cancers?

**Dr. Claudia Henschke:** I think that these patients are at a higher risk than any of our high-risk groups, and they should have a CT scan at least at 1 year and be followed every year thereafter. They have at least 10 years of life expectancy left, on average.

**Dr. Lynch:** So you do it until they’ve shortened their survival to <10 years, which would be ~86 for women and 81 for men! The question is, after 10 years, what do you do? I follow them yearly up until 10 years, and at that point, many of them choose to go back to their internist.

**Dr. Henschke:** They have the same risk of new primaries.

**Dr. Johnson:** The information that exists indicates that beyond 5 years, the risk per year is at least as high, maybe twice as high, as years 1 to 5. I don’t know of any data after 10 years. There’s no information to say that you can follow-up any less often.

**Dr. Lynch:** Our chest surgeons still get chest X-rays every 6 months despite my getting a chest CT every year, and they argue that you have to get the chest X-ray. Dr. Wood, you practice at Mass General. What is that X-ray done for?

**Dr. Douglas Wood:** In the first 2 to 3 years, the surgeon is following for signs of resectable or otherwise treatable recurrent disease. That is very different from what you are looking for with spiral CT over a longer time frame, where you are viewing them as the highest risk population for a new primary tumor. In terms of the times involved, you are much more likely to get a recurrence within the first 2 years, and radiologic findings may change significantly within a 2- to 4-month time span, whereas longer time intervals are reasonable during surveillance for a new primary cancer.

**Dr. Henschke:** As a radiologist, I would say that a postsurgical chest X-ray is of limited value, other than for pneumonia and pneumothorax. If you are looking for a recurrence or a new primary, the best way to see that is to have one CT scan as a baseline at 6 months or later, then do it every year. I can’t understand why the surgeon is asking for the chest X-ray.

**Dr. Malcolm DeCamp:** We’re talking about local recurrences. It’s unlike sitting blinded and looking at X-rays all day. We know exactly where we operated on them and what we are looking for. I actually agree with ordering the X-ray.

**Dr. Henschke:** The more you know, the clearer you’ll see it on the CT.

**Dr. DeCamp:** I’m trying to be cost-effective.

**Dr. Wood:** I would agree that it’s much clearer to see it on a CT scan, but a 1-year follow-up CT scan is too far out because if they are going to have a local recurrence, there is a difference between detecting it at 4 months and detecting it at 1 year, in the potential for being able to effectively treat them for salvage curative intent surgery.

**Dr. Henschke:** I would say, at 6 months, you have enough of the postsurgical changes that you can really interpret that CT fairly effectively, as a radiologist. Then you’d do it every year thereafter.

**Dr. Lynch:** I do exactly what you say, Dr. Henschke. I get the first CT about 4 months after surgery unless they are going on
adjuvant therapy, in which case we get it a little bit earlier. But
at 4 months, as everyone knows, that CT is going to have
something on it, and the radiologist is going to say, “Small,
ground-glass opacity found on the left lower lobe. Recommend
3-month interval follow-up.” So you end up that first year or
two following schmutz a lot more often than for people who
just have had resected lung cancers. I actually don’t mind that
because I agree with Dr. Wood. For those first couple of years,
you are worried about local recurrence. How many of those we
are able to cure, I don’t know. The people with second
primaries whom I’ve cured were 4 or 5 years out.

Dr. James Jett: I do a CT scan once a year as well. Anecdotally,
we’ve picked up a couple of nodules we’ve resected and a couple
of mediastinal recurrences that we’ve biopsied, then treated with
chemoradiation. I have several of these patients who are out 3 or
4 years. But it’s anecdotal.

Dr. Lynch: Let me ask for a show of hands on this scenario.
Let’s say you have a 54-year-old postsurgical patient who had
a 2 cm moderately differentiated adenocarcinoma, node-
negative. It was not a ground-glass opacity. It’s not BAC. This
patients has some mild COPD, but otherwise feels well. I’d
like to see a show of hands, if the options were close
observation versus four cycles of your favorite platinum-based
regimen. How many people here would vote for observation?
One, two, three, four, five, six, seven, eight. How many
would vote for chemotherapy? Okay, nine. So that tells you
whether we are really making a lot of progress in reaching
consensus.

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