REVIEW ARTICLE

Adjuvant Chemotherapy After Complete Resection of Non-Small Cell Lung Cancer

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SUMMARY

Introduction: In non-small cell lung cancer (NSCLC) surgical resection is the treatment of choice in stages I and II of the disease; but even of this selected group of patients, almost half suffer recurrence following complete resection, usually in the form of distant metastases. The role of adjuvant systemic chemotherapy has been investigated extensively in the last two decades.

Methods: Selective literature review of randomized phase III trials.

Results and discussion: There is currently no indication for adjuvant chemotherapy in patients with stage IA disease, whereas the role of adjuvant chemotherapy for stage IB disease remains controversial. To treat a patient with stage IB disease should be an individualized decision depending on age, tumor size, vascular invasion, and patient preference. Adjuvant chemotherapy is now the standard of care after complete resection of stage II-IIIA NSCLC. Patients considered for adjuvant chemotherapy should be under 75 years of age, have no contraindications to cisplatin-based chemotherapy, and should be in a good performance status after surgery. Currently the standard adjuvant chemotherapy regimen is a combination containing cisplatin and vinorelbine.

Dtsch Arztebl Int 2008; 105(14): 249–54
DOI: 10.3238/arztebl.2008.0249

Key words: adjuvant chemotherapy, cisplatin, non-small cell lung cancer, phase III trials, vinorelbine

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Adjuvant chemotherapy after complete resection of a solid tumor aims to reduce the risk of local recurrence and prolong overall survival. This can be achieved by eliminating existing systemic micrometastases and disseminated tumor cells present at the time of the operation, and by improving local control.

Adjuvant therapeutic strategies have become established in breast cancer, colorectal cancer, ovarian cancer, and small cell lung cancer. They improve 5-year survival rates by 3 to 10% in absolute terms (1–6).

Because of its increasing incidence, lung cancer presents a particular oncological challenge. Histopathologically, a differentiation is made between non-small cell cancers (85% of cases) and small cell cancers (15%). The prognosis of patients with non-small cell lung cancer (NSCLC) is poor, with a 5-year survival rate of 10 to 15%. Even in patients with localized tumors of stages I (T1/2, N0, M0) and II (T1/2, N1, M0, and T3, N0, M0) without mediastinal lymph node metastases, the cancer recurs on average in half of the patients after complete resection (R0 resection) (stage IA 33%, IB 43%, IIA 45%, IIB 61%); in 85% of cases this recurrence manifests as distant metastases (7). For this reason, a possible role of postoperative adjuvant chemotherapy in NSCLC has been studied intensively over the past two decades.

This article gives an overview over current trials and the current data situation for adjuvant chemotherapy in NSCLC, but also aims to provide concrete therapeutic recommendations. The authors evaluated randomized phase III trials of adjuvant chemotherapy that were conducted and published in the past 15 years.

Overview

The first tendency of an advantage of adjuvant chemotherapy was shown in a meta-analysis published in 1995, which evaluated 8 studies with regard to the effects of adjuvant chemotherapy using cisplatin (8). Cisplatin therapy resulted in an absolute improvement in 5-year survival rates of 5% compared with observation alone. This difference did, however, not reach significance ($p = 0.08$) (8).

Studies such as the ALPI study (9) or the big lung cancer study (10), which combined cisplatin mainly with first generation cytotoxic drugs (mitomycin C, ifosfamide, vindesine, vinblastine), found no significant survival advantage *(table)*.

In January 2004, the IALT study was published – the first study to show a significant survival advantage for patients treated with adjuvant chemotherapy. This study is the largest so far, with 1867 patients (median age 59), and compared cisplatin based dual combination chemotherapy (start within 60 days postoperatively) with observation alone. The study included patients with pathological tumor stages I to III (11). Cisplatin was combined with etoposide, vinorelbine, vinblastine, or vindesine. The administered cisplatin dose was 80 to 120 mg/m^2 per cycle, with 3 or 4 cycles planned. The patients receiving adjuvant chemotherapy had a significantly higher survival rate (44.5%) than those in the observation arm (40.4%, $p<0.03$, median postobservation period 56 months). 74% of patients who had chemotherapy received a cumulative dose of a minimum of 240 mg/m^2 cisplatin. A subgroup analysis planned before the start of the study showed that patients whose general performance status postoperatively was poor and patients with early tumor stages (IA) did not benefit from adjuvant chemotherapy. In 22.6% of patients, chemotherapy resulted in at least one episode of grade IV toxicity (neutropenia 17.5%, thrombocytopenia 2.6%, vomiting 3.3%) (11).

The intergroup study JBR.10 of the National Cancer Institute of Canada (NCIC), which included 482 patients (median age 61) with completely resected NSCLC of stages IB or II A/B (except for T3N0M0), combined adjuvant chemotherapy with cisplatin and vinorelbine with observation alone (12). The patients who had been randomized into the chemotherapy arm received cisplatin 50 mg/m^2 on days 1 and 8 and vinorelbine 25 mg/m^2 on days 1, 8, 15, and 22 (repeat on day 29). Adjuvant chemotherapy was started within 6 weeks postoperatively (12). At 62 months follow-up, the patients who had had chemotherapy had a significantly longer overall survival than patients in the observation arm (median survival 94 versus 63 months, $p = 0.009$; 5-year survival rate 69% versus 54%, $p = 0.03$). The planned four cycles of chemotherapy could be given to only half of the patients in the chemotherapy arm without a reduction in dosage. The most common toxicity was neutropenia with a grade III/IV toxicity in 73% of patients. Further grade III/IV toxicities included anemia in 7% of patients, thrombocytopenia in 1%, fatigue in 15%, anorexia in 10%, nausea in 10%, vomiting in 7%, and neuropathy in 3%. The patients who had had to have pneumectomies had notably more frequent and severe chemotherapy related side effects than those who had had only lobectomies (66% versus 34% of toxicity grade III/IV) (12).

An age dependent analysis of the NCIC intergroup study JBR.10 that was presented at the American Society of Clinical Oncology (ASCO) congress in 2006 showed that patients older than 65 benefited significantly from adjuvant chemotherapy ($p = 0.04$) (13). However, survival in patients aged 75 or older was significantly shorter than in patients aged 66 to 74 (13).

TABLE

Overview of randomized phase III studies of adjuvant cisplatin based chemotherapy versus observation in non-small cell lung cancer

Study	Tumor stage	No of patients	Chemotherapeutic regimen/ No of cycles	Median follow-up in months	Median survival in months: chemotherapy versus observation	5 year survival rate: chemotherapy versus observation
ALPI (9)	p I–IIIA	1209	Cisplatin + mitomycin C + vindesine; 3 cycles	64.5	55.2 vs. 48 p = 0.6	No data
BLT (10)	p I–III	381	Cisplatin + mitomycin C + ifosfamide or Cisplatin + mitomycin C + vinblastine or Cisplatin + vindesine or Cisplatin + vinorelbine; 3 cycles	34.6	33.9 vs. 32.6 p = 0.9	No data
IALT (11)	p I–III	1867	Cisplatin + etoposide or Cisplatin + vinorelbine or Cisplatin + vinblastine or Cisplatin + vindesine; 3–4 cycles	56	No data	44.5 % vs. 40.4 % p < 0.03
Intergroup JBR.10 of NCIC (12)	p IB–IIB (without T3N0M0)	482	Cisplatin + vinorelbine; 4 cycles	62	94 vs. 63 p = 0.009	69 % vs. 54 % p = 0.03
ANITA (14)	p IB–IIIA	840	Cisplatin + vinorelbine; 4 cycles	> 70	65.7 vs. 43.7 p = 0.02	51 % vs. 43 % p = 0.02

The pooled analysis (LACE, lung adjuvant cisplatin evaluation) of the data from the 5 studies using cisplatin based chemotherapy (BLT, ALPI, IALT, NCIC JBR.10, ANITA) including 4584 patients showed an absolute 5 year benefit of 4.2% for the patients treated with cisplatin (15).

The regimen of cisplatin and vinorelbine was also tested in the ANITA study (14). 840 patients (median age 59) with completely resected NSCLC of stages IB/IIA/B, or IIIA were included in the study. Patients were randomized into an observational arm and into an arm receiving adjuvant chemotherapy (cisplatin 100 mg/m^2 on days 1, 29, 57, and 85; and vinorelbine 30 mg/m^2/week with 16 doses in 20 weeks). The chemotherapy regimen was started within 42 days postoperatively. With a median postobservation period of more than 70 months, chemotherapy with cisplatin and vinorelbine resulted in a significantly prolonged overall survival compared with observation alone (median survival 65.7 months versus 43.7 months, p = 0.017; 5-year survival rate 51.2% versus 42.6%). 85% of patients having chemotherapy developed neutropenias of toxicity grade III/IV; 9% were febrile. Further grade III/IV toxicities included anemia in 14% of patients, thrombocytopenia in 3%, asthenia in 28%, anorexia in 15%, nausea or vomiting in 27%, and neuropathies in 3%. The median dose intensity was 89% of the planned dose for cisplatin and only 59% for vinorelbine (14).

A pooled analysis of five studies (big lung trial, ALPI, IALT, NCIC JBR. 10, ANITA) including a total of 4584 patients that was published in 2006 and compared cisplatin based chemotherapy with observation alone showed a significantly decreased risk of death (hazard ratio [HR] = 0.89, p<0.005) for patients who had received cisplatin over a median observation period of 5.1 years (15). This corresponds to an absolute improvement in 5-year survival of 4.2%. Subgroup analysis showed no benefit of adjuvant chemotherapy with cisplatin for patients with a pathological tumor stage IA (HR = 1.41) and for stage IB only a small, non-significant advantage (HR = 0.93). The benefits was most obvious for tumor stages II and III (HR = 0.83) (15).

Radiotherapy after completed chemotherapy was used in the IALT and ANITA studies in some 20% of patients. The ANITA study showed a survival advantage owing to radiotherapy in the chemotherapy arm and the observation arm, which was most pronounced in patients with a positive N2 lymph node status.

In contrast to the studies mentioned thus far, study 9633 of the Cancer and Leukemia Group B (CALB 9633) used carboplatin instead of cisplatin (16). This was used in combination with the taxane paclitaxel. The study included 344 patients (median age 61) with tumor stage IB. Within 4 to 8 weeks after complete tumor resection, participants were randomized into the observation or chemotherapy arms (4 cycles of paclitaxel 200 mg/m^2 on day 1 and carboplatin AUC6 on day 1, repeated on day 22). After an observation period of 54 months, no significant advantage in terms of overall survival was seen after adjuvant chemotherapy (HR = 0.80, p = 0.10). For the 3-year survival rate, a significant advantage had been seen for chemotherapy patients (p = 0.045), but for the 5-year survival rate this had disappeared (60% versus 57%; p = 0.32). A significant advantage for adjuvant chemotherapy with paclitaxel and carboplatin was, however, seen for median disease free survival (HR = 0.74, p = 0.027) (16). A subgroup analysis suggests that patients with tumor sizes of more than 4 cm and/or invasion of the lymphatic vessels (L1) benefit from adjuvant chemotherapy.

Compared with cisplatin containing regimens, the combination of carboplatin and paclitaxel was better tolerated. 4 cycles of chemotherapy were administered in 85% of patients (55% without dose reduction and 30% with dose reduction). Neutropenias of toxicity grade III/IV were found in 36% of patients (16).

Several randomized studies were conducted in Japan that investigated the oral 5-fluorouracil derivate UFT (tegafur plus uracil) (17–22). UFT has a favorable side effect profile and was administered to patients as adjuvant therapy after complete tumor resection, daily and orally, for 1 or 2 years. Since only some of the studies showed an advantage for adjuvant UFT therapy, a meta-analysis was conducted in 2005 that included 6 UFT studies from Japan (23). Of the patients included in the meta-analysis, 80% had an adenocarcinoma, and almost all patients had tumors of stage I (two thirds IA, one third IB). The meta-analysis showed that adjuvant therapy with UFT resulted in significantly higher 5-year and 7-year survival rates in Japanese patients with stage I adenocarcinomas than observation alone (23).

BOX 1

Indications and conditions for adjuvant chemotherapy in patients with non-small cell lung cancer

Indications:

- No indication in stage IA (confirmed data)
- Decision in stage IB in the individual patient (data not unequivocal)
- Postoperative tumor stage IIA-IIIA (confirmed indication)

Prerequisites:

- R0 resection
- Good general postoperative performance status (ECOG performance status 0 to 1)
- Age <75
- No comorbidities that rule out cisplatin based chemotherapy
- Start of chemotherapy 4 to 6 weeks (maximum 8 weeks) postoperatively

Current therapeutic recommendations

Taking current studies into consideration, the recommendation should be for patients with tumor stages IIA or IIB after total tumor resection (R0 resection) to

BOX 2

Adjuvant chemotherapeutic regimen in non-small cell lung cancer

- Chemotherapeutic regimen: cisplatin+vinorelbine
- Possible modern dosage schemes:
  - Cisplatin 80 mg/m^2 on day 1 + vinorelbine 25 mg/m^2 on days 1 and 8; repeated on day 22
  - Cisplatin 40 mg/m^2 on days 1 and 8 + vinorelbine 25 mg/m^2 on days 1 and 8; repeated on day 22
  - Cisplatin 50 mg/m^2 on days 1 and 8 + vinorelbine 25 mg/m^2 on days 1, 8, and 15, repeated on day 29
- Number of cycles: 4 (if poorly tolerated then fewer cycles; a cumulative dose of cisplatin of 240 mg/m^2 should be the target, however)
- Optimum start: 4–6 weeks (8 weeks at the latest) postoperatively

have adjuvant chemotherapy (recommendation grade A, level of evidence I) *(box 1)*. The same holds true for patients with incidental stage IIIA tumors (in whom the positive lymph node status was not known before surgery and was only detected postoperatively on histology) or patients with tumor before primary surgery (i.e., a known positive lymph node in an ipsilateral mediastinal location). In all other patients with stage IIIA tumors, neoadjuvant preoperative induction chemotherapy alone or combined with radiotherapy is to be preferred to adjuvant postoperative chemotherapy. According to current data, no indication for adjuvant chemotherapy exists for patients with grade IA tumors.

The data situation is not so clear for tumor stage IB, so that at this time, no definitely recommendation regarding adjuvant chemotherapy can be made, and decisions for these patients will have to be made on an individual basis until further data become available. Criteria for a decision for this treatment in tumor stage IB might be a tumor size of >4 cm, lymphatic (L1) or venous invasion (V1), young age or young biological age, and/or a strong desire on the part of the patient to be treated.

In general, adjuvant chemotherapy should be suggested only to those patients with a good general postoperative performance status, who are younger than 75, and who have no comorbidities (for example, impaired renal function, impaired hearing, heart failure NYHA stages III and IV) that would rule out cisplatin therapy. The start of adjuvant chemotherapy would be 4 to 6 weeks – a maximum of 8 weeks – after the operation. If adjuvant radiotherapy is planned for stage IIIA then this is to be given after adjuvant chemotherapy *(box 1)*.

The benefits of adjuvant chemotherapy have been shown only for cisplatin based chemotherapy *(table)*. Carboplatin should therefore be used only in study settings. Most of the available data show an advantage for adjuvant chemotherapy with cisplatin and vinorelbine, so that this dual combination is to be regarded as standard therapy. The combination of cisplatin and other third generation cytotoxic drugs – such as gemcitabine, docetaxel, or paclitaxel – combinations without cisplatin, and molecular targeted therapy should be provided only in the context of studies. The same is true for UFT, whose benefits have to date been shown only in Japanese study populations. Because of possible pharmacogenomic and molecular differences, the Japanese results cannot simply be applied to European and North American populations.

A desirable target is the administration of 4 therapeutic cycles of cisplatin and vinorelbine. If a patient does not tolerate chemotherapy then a lower number of cycles should be decided on an individual basis and taking into account the benefit-risk balance. A cumulative dose of cisplatin of 240 mg/m^2 is desirable.

To reach a high dose intensity of the cytotoxic drugs administered and to avoid reduction in dosages, a modified (compared with earlier years) dosage scheme for cisplatin and vinorelbine should be adhered to that is better tolerated *(box 2)*. Recommended dosages are cisplatin 80 mg/m^2 on day 1 and vinorelbine 25 mg/m^2 on days 1 and 8, every three weeks. Alternatively, therapeutic regimens with a split dosage of cisplatin may be used – for example, the modified regimen from the NCIC intergroup study JBR.10 (cisplatin 50 mg/m^2 on days 1 and 8 and vinorelbine 25 mg/m^2 on days 1, 8, and 15, every four weeks) or alternatively, cisplatin 40 mg/m^2 on days 1 and 8 and vinorelbine 25 mg/m^2 on days 1 and 8 every three weeks *(box 2)*.

Therapeutic regimens using a split dose of cisplatin make sense especially in patients in whom no high volume load is advisable during prehydration or posthydration during cisplatin administration because of e.g. a pneumectomy.

Because of the high emetogenic potential of cisplatin, each administration should be accompanied by standard antiemetic treatment, consisting of an HT3 antagonist, dexamethasone, and a neurokinin-1 antagonist.

Most patients who have undergone curative surgery for colorectal cancers or breast cancers have a good general performance status. This is vastly different in postoperative patients with NSCLC. These patients often have relevant comorbidities, such as chronic obstructive pulmonary disease or coronary heart disease. Especially those patients who have had pneumectomies often have more frequent and more severe chemotherapy induced side effects, as well as poorer compliance with adjuvant chemotherapy as those in whom the loss of lung parenchyma is small (24). The chemotherapeutic treatment of postoperative patients with NSCLC therefore presents a particular challenge and should be administered only in – or in close cooperation with – centers with long term interdisciplinary experience in the multimodal therapy of lung cancer *(box 3)*.

Outlook

In the coming years, predictors will need to be defined – taking into account molecular genetic and molecular biological findings – that will, in addition to the anatomical tumor stage, enable individual categorization of patients into more specific prognostic groups. As with breast cancer it may then become possible to determine – on the basis of a special marker profile – every operated NSCLC patient's individual recurrence risk and administer targeted adjuvant chemotherapy on this basis. Future developments in adjuvant systemic therapy of patients with NSCLC are certain to modify the newly established standard. To enable rapid further progress in adjuvant therapy of patients with NSCLC, treating such patients in the context of large randomized controlled studies is required.

Further information about adjuvant chemotherapy for NSCLC is available in the consensus statement of the interdisciplinary expert meetings of 3 to 4 June 2005 in Hamburg and 13 September in Frankfurt on the homepage of the German Cancer Society, at www.krebsgesellschaft.de.

BOX 3

Clinical conclusions

1. An indication for chemotherapy exists not only in inoperable locally advanced (stage IIIB) and distant metastatic (stage IV) non-small cell lung cancer, but chemotherapy is an integral part of the therapeutic concept in localized tumor stage II and in operable locally advanced disease (stage IIIA).
2. The chemotherapeutic treatment of operated patients with NSCLC presents a particular challenge and should be conducted only in – or in close cooperation with – centers with long term interdisciplinary experience in multimodal therapy of lung cancer.
3. In patients who – after complete resection of their lung cancer – meet the criteria for adjuvant chemotherapy, subsequent curative treatment or rehabilitation measures and the start of chemotherapy will have to be carefully coordinated.

Conflict of interest statement
The authors declare that no conflict of interest exists according to the guidelines of the International Committee of Medical Journal Editors.

Manuscript received on 15 June 2007; revised version accepted on 4 December 2007.

Translated from the original German by Dr Birte Twisselmann.

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