Gemcitabine combined with cisplatin as neoadjuvant chemotherapy in stage IB–IIIA non-small cell lung cancer

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This single-arm, multicenter, phase II study examined the objective response rate and toxicity after neoadjuvant chemotherapy with gemcitabine and cisplatin in patients with stage IB–IIIA non-small cell lung cancer. Treatment consisted of three 21-day cycles of gemcitabine (1000 mg/m^2) on days 1 and 8 and cisplatin (75 mg/m^2) on day 1 of each cycle. Surgery was performed 4–5 weeks after day 1 of the last cycle of study therapy. A total of 52 patients from five investigative sites in Russia were enrolled in the study, of which 50 (96.2%) received study therapy. Of the 49 patients who were evaluable for response, six (12.2%) had a complete response and 16 (32.7%) had a partial response, resulting in an overall response rate of 44.9%. Disease progression occurred in four out of the 49 (8.2%) patients. Radical tumor resection was performed in 38 out of the 49 (77.6%) patients. A total of 41 patients were assessed for a pathological complete response, of which four (9.8%) patients had pathological complete tumor regression. Postsurgical restaging was performed in 36 out of the 41 (87.8%) patients. Tumor downstaging occurred in 16 out of the 36 (44.4%) patients. Grade 3/4 neutropenia and thrombocytopenia were experienced by 28.0/6.0% patients and 6.0/2.0% patients, respectively. Grade 3 anemia occurred in 4.0% of the patients. Nonhematological toxicity was mild. Overall mortality was 30.0% (15 out of 50 patients), predominantly from progressive disease. The 1-year overall survival rate was 74.4% (95% confidence interval: 61.3–87.6%). Neoadjuvant chemotherapy with gemcitabine and cisplatin showed a good safety profile with an encouraging possibility of curative surgery in patients with early-stage non-small cell lung cancer. *Anti-Cancer Drugs* 22:569–575 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Approximately 40% of patients with non-small cell lung cancer (NSCLC) present with IB–IIIA stage disease. Most of them are considered to be candidates for curative local therapy, predominantly surgical resection. However, long-term survival in patients treated with a single therapeutic option (chemotherapy, radiotherapy, or surgery) is poor, with local recurrence and distant metastases being the major cause of death [1]. Two treatment strategies, neoadjuvant/induction and adjuvant chemotherapy, are used to control locoregional and systemic disease and to improve survival [2–6]. The theoretical advantages of neoadjuvant therapy include its potential to increase the subsequent surgical resection rate and to reduce the rate of distant relapse owing to the eradication of micrometastases [7]. Furthermore, neoadjuvant chemotherapy has a relatively high compliance rate compared with adjuvant treatment, provides unimpeded drug delivery to the tumor because vasculature is unaffected by surgery or radiotherapy, and enables the in-vivo assessment of response to identify patients who will potentially benefit from adjuvant chemotherapy [5,8,9].

After the encouraging results of early clinical trials in patients with stage IIIA–N2 NSCLC, the concept of neoadjuvant chemotherapy followed by surgery found general acceptance [10,11]. However, a trial by the French Thoracic Cooperative Group indicated that induction chemotherapy had a more positive effect in stage I and II disease [12]. The results of subsequent studies are rather controversial. Despite containing a large proportion of stage I patients (61%), the largest trial of induction chemotherapy did not show a survival benefit, whereas the Chemotherapy in Early stages NSCLC Trial, which examined the efficacy of induction chemotherapy with gemcitabine and cisplatin in early-stage NSCLC, showed a survival benefit in the subgroup of patients with IIB–IIIA disease, but did not confirm the positive impact of induction chemotherapy in patients with earlier-stage disease [13,14]. A meta-analysis carried

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out by Nakamura *et al.* [14] showed survival differences at 1 and 3 years (but not at 5 years) between bimodal treatment (preoperative chemotherapy and surgery) and surgery alone. However, when only patients with stage IIIA disease were analyzed, no significant difference was observed [15].

Platinum-based doublets with third-generation agents have been extensively studied in the induction setting, but the optimal induction regimen remains to be determined. Gemcitabine has shown synergy with platinum compounds in preclinical tumor models, and these agents are widely used in the treatment of advanced NSCLC. The combination of gemcitabine and cisplatin has been shown to be safe when used in patients with advanced NSCLC with encouraging activity [16–18]. Recently, results from several studies that examined the efficacy and safety of neoadjuvant therapy with gemcitabine and cisplatin or carboplatin have been published [19–21]. This study commenced before these studies were published, and was designed to examine the efficacy of neoadjuvant chemotherapy with gemcitabine and cisplatin in terms of the clinical response rate and pathological complete response rate (pCR) in patients with early-stage (IB–IIB) or locally advanced (IIIA) NSCLC. The tolerability of the study regimen and secondary time-to-event efficacy variables was also assessed.

Patients and methods

Patient selection

Patients aged above 18–65 years with clinical stage IB–IIIA NSCLC, amenable to curative surgical resection, with no earlier tumor therapy, measurable disease, adequate organ function, and 0–1 Eastern Cooperative Oncology Group performance status, were eligible. Written informed consent was obtained from all patients before enrollment. The study protocol was approved by the appropriate ethics review boards and was conducted according to good clinical practice guidelines and the Declaration of Helsinki.

Study objectives

The primary objective of the study was to assess the clinical response rate after induction chemotherapy with gemcitabine and cisplatin. Evaluation of safety (toxic profile, perioperative and postoperative mortality), pCR, complete tumor resection rate, and time-to-event efficacy variables [time to documented disease progression (TTDP), disease-free survival (DFS), and overall survival] was the secondary objective of the study.

Study treatment

Gemcitabine was given as an intravenous infusion over approximately 30 min at a dose of 1000 mg/m^2 on days 1 and 8 of each 21-day cycle. Cisplatin was given intravenously at a dose of 75 mg/m^2 on day 1 of each cycle after gemcitabine. Study therapy continued up to a maximum of three cycles or until progressive disease, unacceptable toxicity, or another permitted reason for premature study therapy discontinuation. A computed tomography (CT) scan was performed 15–22 days after day 1 of the last cycle of study therapy. Patients underwent surgery 29–36 days after day 1 of the last cycle of study therapy if the CT scan indicated anatomical resectability and the patients were considered to be adequately fit for radical NSCLC surgery. It was recommended that patients who did not qualify for radical NSCLC surgery should receive radical or palliative radiotherapy (> 3 weeks from last dose of study therapy), as clinically indicated.

Dose adjustments

No dose escalations were allowed. The dose of gemcitabine was reduced by 25% on day 8 if the neutrophil count was between 1.0 and less than 1.5×10^9/l and if the platelet count was 75–99×10^9/l. The dose of gemcitabine was omitted on day 8 if the neutrophil count was less than 1.0×10^9/l and the platelet count was less than 75×10^9/l. Study treatment was discontinued in the event of documented grade 3 or higher pulmonary toxicity. In the event of other grade 3 nonhematological toxicities (excluding nausea, vomiting, and alopecia), the dose of gemcitabine on day 8 was reduced by 25% or delayed. In the event of grade 4 nonhematological toxicities (excluding alopecia), the dose of gemcitabine on day 8 was omitted. Investigators were required to decide whether the dose of gemcitabine should be reduced by 25% or withheld on day 8 for patients who had a grade 3 nonhematological toxicity between day 1 and day 8 (excluding nausea and vomiting).

Study treatment could be postponed for up to 4 weeks if a patient had not recovered from hematological and/or nonhematological toxicity at the beginning of a cycle (day 1). Study treatment could recommence immediately after neutrophil ($\geq 1.5 \times 10^9$/l) and platelet ($\geq 100 \times 10^9$/l) recovery. Patients were discontinued from the study if a cycle had to be postponed owing to toxicity for more than 4 weeks. In the event of grade 4 neutropenia, thrombocytopenia, or febrile neutropenia or if the next cycle had to be delayed by more than 1 week owing to toxicity, the dose of gemcitabine was reduced to 800 mg/m^2 on days 1 and 8 and the dose of cisplatin was reduced to 60 mg/m^2 on day 1. Full supportive care therapies were permitted during the study, but the concomitant use of any other antitumor therapy was not permitted while the patients were receiving study therapy. The routine use of colony-stimulating factors was not permitted.

Study assessments

Baseline assessments included a chest radiograph and a CT scan of the thorax. Additional investigations (mediastinoscopy or PET scan) were performed to exclude N3

and M1 disease. A CT scan of the thorax was taken between days 15 and 22 of the third cycle for tumor measurement and preoperative tumor assessment, and in the first cycle in case of early study drug discontinuation. After surgery (or radical radiotherapy if a patient was medically unfit for NSCLC surgery) patients had tumor assessments every 2 months until 12 months after surgery (or the start of radiotherapy), tumor recurrence, or death, whichever occurred first.

Dose intensity evaluation

Dose intensity was defined as the cumulative dose of study drug divided by the duration of chemotherapy (time interval from the first dose of study drug until 21 days after the last study dose). The relative dose intensity was defined as dose intensity actually received by patient, relative to the planned dose to be received during 3-week cycles and expressed as percentage.

Efficacy evaluations

The clinical tumor response rate was defined by the World Health Organization's response criteria [22]. The pCR rate was a secondary efficacy endpoint in this study. A pCR was defined as the absence of any viable tumor cells in resected tumor specimens on histological examination of the primary tumor and lymph nodes. The pCR rate was defined as the number of patients with a documented histological complete response divided by the number of patients who qualified for the pCR analysis (any patient who underwent surgery after receiving at least two cycles of study therapy). The complete tumor resection rate was defined as the number of patients with complete tumor resection divided by the number of patients who were enrolled in the study and met the eligibility criteria. TTDP was defined as the time from the date of enrollment to the first date of documented disease progression. Overall survival was defined as the time from the date of study enrollment to the date of death from any cause. DFS for operated patients was defined from the date of surgery to the first documented recurrence or death from any cause, whichever occurs first.

Safety evaluations

Safety parameters were assessed according to the National Cancer Institute Common Toxicity Criteria (version 2.0). Perioperative mortality included deaths that occurred during the interval from day 22 of the last chemotherapy cycle until the date of surgery. Postoperative mortality included deaths that occurred during the time between 2 and 31 days after the operation. Intraoperative mortality included deaths that occurred during the operation and the day after the operation.

Statistical analyses

The target enrollment was 50 patients. A sample size of 50 patients would provide 87% power to detect a clinical response rate of 80% at the 5% significance level. All enrolled patients who met the eligibility criteria were evaluated for clinical response rate if they had measurable disease and received at least one cycle of study therapy. Enrolled patients who met the eligibility criteria were included in the pCR analysis if they underwent surgical tumor resection after receiving at least two cycles of study therapy. All enrolled patients who met the study's eligibility criteria were included in the analysis of the complete tumor resection rate and the time-to-event secondary efficacy measures. The time-to-event variables were estimated using the Kaplan–Meier method [23]. All patients who received at least one dose of study therapy were included in the safety analyses. Patients who received at least one dose of study therapy and were considered to be operable were evaluated for perioperative mortality and DFS. Patients who underwent surgery after receiving at least one dose of study treatment were included in the 30 day-postoperative mortality analysis. Deaths during the first day after the operation were counted separately. Statistical analyses were conducted using SAS Software (version 8.02, SAS Institute, USA).

Results

Patient disposition

From December 2002 until February 2005, 52 patients who were untreated earlier from five investigative sites in Russia were enrolled in the study. Fifty (96.2%) of these patients were assigned to study therapy, 44 out of the 52 (84.6%) patients completed the study according to the protocol, and eight out of the 52 (15.4%) patients discontinued the study prematurely. The reasons for premature study discontinuation included patient decision ($n = 3$), ineffective therapy ($n = 2$), physician's decision ($n = 1$), protocol violation ($n = 1$), and death ($n = 1$). Forty-nine (94.2%) patients were included in the analyses of clinical response rate, complete tumor resection rate, TTDP, and overall survival. A total of 41 out of the 52 (78.8%) patients were included in the assessment of pCR, DFS, and perioperative and postoperative mortality. Fifty (96.2%) patients were included in the safety analyses. Two patients were excluded from the toxicity assessment because they did not receive study treatment owing to a protocol violation ($n = 1$) or patient's decision ($n = 1$).

Baseline characteristics

Most of the patients were men ($n = 46$, 88.5%) and most patients had an Eastern Cooperative Oncology Group performance status of 1 ($n = 35$, 67.3%) and a pathological classification of either squamous cell carcinoma ($n = 32$, 61.5%) or adenocarcinoma ($n = 18$, 34.6%). The median age of the patients was 53.5 years (range: 37.0–65.0 years). At study entry, 28 out of the 52 (53.8%) patients had stage IB disease, seven (13.5%) patients had stage IIB disease, 16 (30.8%) patients had stage IIIA disease, and one (1.9%) patient had stage IIIB NSCLC. Tumors

were staged as T2 in 41 out of the 52 (78.8%) patients, T3 in 10 (19.2%) patients, and T4 in one (1.9%) patient. No lymph node involvement (N0) was observed in 32 out of the 52 (61.5%) patients, whereas N1 involvement was observed in three (5.8%) patients and 17 (32.7%) patients had N2 involvement. There were no patients with distant metastases. The patient with stage IIIB/N2 disease was inadvertently enrolled and then withdrawn from the study and their results were excluded from the data analyses.

Antitumor activity

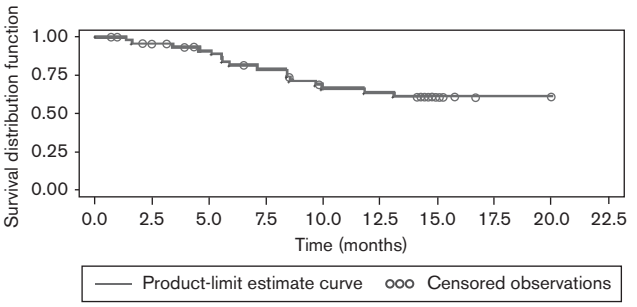
Of the 49 patients who were included in the clinical response rate analysis, six (12.2%) patients had a complete response and 16 (32.7%) patients had a partial response as their best response, resulting in an overall clinical response rate of 44.9%. A total of 19 (38.8%) patients had stable disease as their best response, whereas progressive disease was the best response in four (8.2%) patients. The best clinical response at the time of analysis was not assessable in four out of the 49 (8.2%) patients.

Radical tumor resection was performed in 38 out of the 49 (77.6%) patients, and the complete (radical) tumor resection rate was 77.6% [95% confidence interval (CI): 63.4–88.2%]. A total of 37 out of the 41 (90.2%) patients had no pathological complete tumor response after study therapy. Pathological complete tumor regression was confirmed in four out of the 41 (9.8%) patients, and therefore the pCR was 9.8%. All observations of pCR were made in patients who had stage IB to IIB disease at study entry.

Postsurgical restaging was performed in 36 out of the 41 (87.8%) patients. Tumor downstaging (TNM) was observed in 16 out of the 36 (44.4%) patients. In patients with IIIA/N2 stage NSCLC, downstaging was observed in nine out of the 12 (75.0%) analyzed cases, but no pCR was observed.

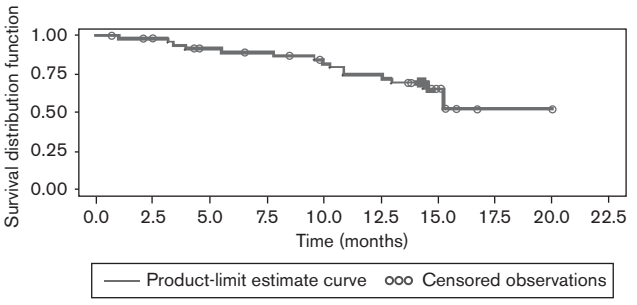
Disease progression during the study period occurred in 16 out of the 49 (32.7%) patients. The median TTDP during the study's follow-up period was not reached. The 1-year assessment of TTDP was 63.7% (95% CI: 48.9–78.5%) (Fig. 1). Fifteen (30.6%) out of the 49 patients in the overall survival analysis population died during the study period. Figure 2 shows the Kaplan–Meier curve for overall survival. Median overall survival was not reached during the study's follow-up period. One-year overall survival was 74.4% (95% CI: 61.3–87.6%), and 1.5-year overall survival was 52.3% (95% CI: 26.3–78.3%). Fifteen (36.6%) out of the 41 patients in the DFS analysis population died during the study period. Figure 3 shows the Kaplan–Meier curve for DFS. Median DFS during the study's follow-up period was not reached. One-year DFS was 61.8% (95% CI: 46.5–77.0%).

Fig. 1



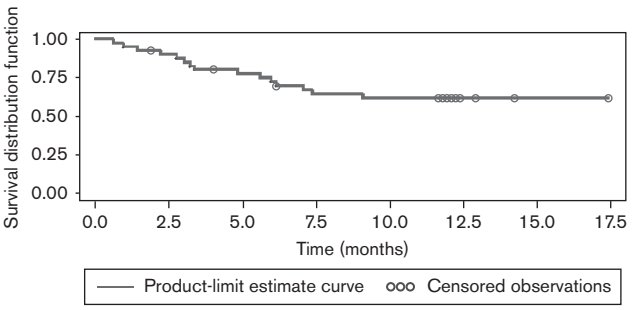
Time to documented disease progression (months).

Fig. 2



Overall survival (months).

Fig. 3



Disease-free survival (months).

Dose delays, dose reductions, and dose intensity

A total of 145 cycles of study therapy were given. All of the 50 treated patients received at least two cycles of study therapy and 45 out of the 50 (90.0%) patients received three cycles of study therapy. The median dose intensity was 95.2 mg/m^2/day for gemcitabine and 3.6 mg/m^2/day for cisplatin, which was in line with the target dose intensity for each drug. The median relative dose intensity was 100% for both drugs. Study treatment was delayed in seven out of the 145 (4.8%) cycles and in six out of the 50 (12.0%) patients, and four out of the 145

(2.8%) cycles were delayed owing to hematological toxicity. One (2.0%) patient was given a reduced dose of both study drugs in one cycle owing to hematological toxicity. The day 8 dose was delayed in 11 out of the 145 (7.6%) cycles in eight out of the 50 (16.0%) patients, and dose reductions occurred on day 8 in eight out of the 145 (5.5%) cycles for seven out of the 50 (14.0%) patients.

Toxicity

The most common hematological toxicity was neutropenia (Table 1). Grade 3 neutropenia occurred in 14 out of the 50 (28.0%) patients and grade 4 neutropenia was observed in three out of the 50 (6.0%) patients. There were no cases of febrile neutropenia. Grade 3 thrombocytopenia occurred in three out of the 50 (6.0%) patients and grade 4 thrombocytopenia was observed in one (2.0%) patient. Grade 3 anemia occurred in two (4.0%) patients (Table 1).

The rate of nonhematological toxicity (predominantly gastrointestinal) was predominantly mild and did not exceed grade 2 (Table 2).

Total mortality was 30.0% (15 out of the 50 patients), with one death resulting from acute stroke before operation, two postoperative deaths of 41 (4.9%) operated patients as a result of surgical complications, and 12 deaths of the 50 (24.0%) patients as a result of progressive disease during the follow-up period. There were no perioperative or intraoperative deaths.

Table 1 The frequency of grades 3 and 4 treatment-related hematological toxicities ($N=50$)

	Grade 3		Grade 4	
Toxicity	*n*	Percentage	*n*	Percentage
Neutropenia	14	28	3	6
Leucopenia	4	8	0	0
Anemia	2	4	0	0
Thrombocytopenia	3	6	1	2

Table 2 Treatment-related nonhematological toxicities ($N=50$)

Toxicity	*n*	Percentage
Gastrointestinal toxicities		
Nausea	7	14.0
Vomiting	3	6.0
Other nonhematological toxicities		
Fatigue	4	8.0
Headache	3	6.0
Alopecia	2	4.0
Pruritus	2	4.0
Rash/desquamation	2	4.0
SGPT (ALT) elevation	2	4.0
SGOT (AST) elevation	1	2.0
Creatinine elevation	1	2.0
Hearing disturbance	1	2.0
Motor neuropathy	1	2.0
Other[a]	6	12.0

Nonhematological toxicity did not exceed grade 2.
ALT, alanine transaminase; AST, aspartate transaminase; SGOT, serum glutamic oxalacetic transaminase; SGPT, serum glutamic pyruvic transaminase.
[a]Includes: weight loss in two (4.0%) patients, and anorexia, taste disturbance, fever, pneumonia/lung infiltrates in one (2.0%) patient each.

Discussion

During the past two decades, a number of trials have been conducted to examine the efficacy of neoadjuvant chemotherapy in NSCLC patients. The first randomized phase II trials performed in stage IIIA NSCLC patients favored neoadjuvant therapy and were stopped early because of significant survival advantages in the chemotherapy arm [10,11]. In a large randomized phase III trial involving 373 operable NSCLC patients, there was an 11-month improvement in median overall survival with neoadjuvant chemotherapy (mitomycin, ifosfamide, and cisplatin) compared with surgery alone in patients with stage I–IIIA disease [11]. The survival benefit of neoadjuvant therapy was found to be statistically significant ($P = 0.027$) in the subset of patients with stage I–II disease [12]. In the MRC LU22 multicenter, randomized, phase III trial, the overall response rate varied from 56 to 82.6%, in patients with early-stage disease [12,13,24]. The overall response rate in this study was lower (44.9%), possibly owing to the more heterogenous study population with a majority of early-stage patients.

The complete surgical resection rate, the pCR rate, and the degree of tumor downstaging are known to be important predictors of long-term survival in patients with stage IIIA of NSCLC [25]. The complete resection rate in our study was 77.6%, which is within the range of complete resection rates reported for recent neoadjuvant studies, ranging from 67.3 to 89.5% [1,20,22,26,27]. We observed tumor downstaging in 44.4% of patients and observed a pCR in 9.8% of patients, which is within the pCR rate reported for other recent studies (2.3–11%) [2–13,20,22,24,26,28].

The results of our study are similar to those reported for the recent Neoadjuvant versus Adjuvant Taxol (paclitaxel)/Carboplatin Hope, in which chemonaive patients with stage I, II, and T3N1 disease were given neoadjuvant chemotherapy with paclitaxel and cisplatin [29]. In the Neoadjuvant versus Adjuvant Carbo Taxol Hope study, the response rate was 55% and the pCR rate was 8% [29]. In our study, the results seem to be more promising in the subgroup of patients with stage IB–IIB NSCLC who had a clinical response rate of 51.4% (18.1% complete response, 33.3% partial response) and a radical resection rate of 81.8%. The pCR rate was the same (9.8%), because pathological complete responses were observed only in the patients with stage IB–IIB disease at study entry.

A limitation of our study was that the patient population was heterogenous and 67.3% of the patients had early-stage disease while 30.8% had stage IIIA NSCLC. Furthermore, all of the stage IIIA patients had mediastinal involvement (N2) at study entry. Patients with locally advanced

(IIIA/N2) NSCLC have already been studied in many neoadjuvant trials, showing good survival results if preoperative treatment led to tumor downstaging [21,22,30–32]. One of the first phase II trials, evaluating stage IIIA NSCLC patients, was published by Van Zandwijk *et al.* [33]. This study examined the efficacy of three cycles of neoadjuvant chemotherapy with gemcitabine and cisplatin before surgery or radiotherapy. The response rate in 47 eligible patients was 70%, including three complete responses. Mediastinal lymph nodes were tumor-free after induction chemotherapy in 53% of the patients who underwent surgery [33].

Girard *et al.* [20] published mature results from a randomized study in patients with stage III/N2 disease who received three cycles of preoperative chemotherapy with gemcitabine and cisplatin (arm A) or preoperative chemotherapy and radiotherapy (cisplatin and vinorelbine followed by radiotherapy 46 Gy; or carboplatin and paclitaxel followed by radiotherapy 46 Gy; arms B and C, respectively). Despite the response rate of 57% in arm A (compared with 82 and 92% in chemoradiotherapy arms B and C, $P = 0.049$), the complete resection rate and pCR were similar in the three arms. Kappers *et al.* [21] retrospectively analyzed data for 99 patients with stage IIIA/N2 disease who were treated with two to four cycles of neoadjuvant chemotherapy with gemcitabine and cisplatin. A total of 39 out of the 99 patients underwent surgery. Mediastinal downstaging was observed in 32 out of the 39 patients. Taking into account the activity of the gemcitabine/cisplatin combination as induction treatment in several trials, there is good reason to consider gemcitabine and cisplatin for induction therapy in patients with early-stage disease [33].

In our study, neither a clinical complete response nor a pCR was observed in the group of patients ($n = 16$, 30.8%) with stage IIIA/N2 disease. Only 68.8% of these patients were completely resected. Nevertheless, tumor downstaging was observed in 75.0% of the resected patients with stage IIIA/N2 disease who were analyzed. In our study, median overall survival was not achieved owing to limited follow-up, but 1-year overall survival was 74.4%, compared with 61–87.2% observed in other studies [20,33,34].

Several investigators who studied preoperative treatment in stage IIIA/N2 disease reported higher morbidity and mortality and lower survival after pneumonectomy compared with lobectomy [35,36]. Kappers *et al.* [21] reported a postoperative mortality of 3% with 1-year mortality of 26% after pneumonectomy and 11% after lobectomy. It was subsequently reported that postsurgical morbidity was not related to neoadjuvant chemotherapy and that neoadjuvant chemotherapy could not be considered to be a risk factor for postoperative mortality [37]. In our study, postoperative mortality was not higher after pneumonectomy compared with lobectomy, and the postoperative mortality rate was 4.9%, which is similar to the results of earlier studies with neoadjuvant chemotherapy (2.9–7%) [10,12,22,28–30,36,38,39].

In our study, the gemcitabine–cisplatin combination had an acceptable toxicity profile and was generally well tolerated [40]. Grade 4 hematological toxicity (neutropenia and thrombocytopenia) occurred in only 2–6% of the patients, indicating that the study therapy regimen generally induced mild myelosuppression. Nonhematological toxicity did not exceed grade 2 and was easily curable. The frequency of hematological teatment-related toxicities was similar in our study to that observed in earlier studies with neoadjuvant chemotherapy with gemcitabine and cisplatin or carboplatin or paclitaxel [20]. Similarly, in a prospective randomized study in patients with potentially resectable clinical stage IIIA NSCLC in China, who received two preoperative cycles of gemcitabine and cisplatin or carboplatin, the main toxicities were hematological (31.5% grade 3–4 thrombocytopenia and 26.3% neutropenia), but there were no cases of hemorrhage, delayed surgery, or perioperative deaths [19].

Potential weaknesses of our study include the short follow-up period, the small number of patients, and the lack of data on initial mediastinoscopy, which could result in disparity between initial clinical data and postoperative histological findings in some patients. The study therapy regimen was active in the treatment of early-stage NSCLC. The pCR rate and radical surgery rate were comparable with the results of similar studies. A total of 77.6% of the patients underwent surgery, which is the optimal treatment for early-stage NSCLC.

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