Final Overall Results of a Study with a Novel Triplet Induction Chemotherapy Regimen (PACCAGE) Followed by Consolidation Radiotherapy in Locally Advanced Inoperable Non-small Cell Lung Cancer (NSCLC)

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Introduction: We report the long term and overall results of a triplet induction chemotherapy regimen followed by standard radiotherapy in patients with locally advanced inoperable stage III non-small cell lung cancer.

Methods: Three cycles of paclitaxel, carboplatin, and gemcitabine were administered every 3 weeks before standard fractionated consolidation radiotherapy starting at least 4 weeks after the last chemotherapy administration. Toxicity and antitumor response was assessed in detail as well as the progression free and overall survival.

Results: Sixty-four patients (25 stage IIIA and 39 stage IIIB) received a total of 179 cycles of chemotherapy. Fifty-six received the planned three cycles. Full-dose radiotherapy was administered in 47 patients (73%), a reduced dose in 11 (17%) and none in six (10%). A 55% objective response rate (OR) (one complete and 34 partial responses) was observed after induction chemotherapy. After completing the whole treatment including radiotherapy, the OR was 40 of 47 evaluable patients (85%). Median time to progression was 10.9 month and median overall survival was 17.2 month, with a significant difference between stage IIIA and stage IIIB patients (23.4 versus 10.5 month; \( p = 0.011 \)). The strongest predictor for a favorable long-term outcome was a metabolic complete response after chemotherapy.

Conclusion: Induction chemotherapy with the paclitaxel, carboplatin, and gemcitabine regimen preceding radiotherapy in patients with locally advanced inoperable stage III non-small cell lung cancer was feasible and active. Radiotherapy could be administered at a full dose in the majority of patients with acceptable toxicity. Long-term survival results of this sequential chemoradiotherapy regimen appear similar to those of concurrent treatment. Patients not achieving a metabolic complete response after induction chemotherapy should be the focus of studies aiming at improved local control.

Key Words: NSCLC, Locally advanced (stage III), Induction Chemotherapy, Radiotherapy.

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Non-small cell lung cancer (NSCLC) frequently presents in a locally advanced inoperable stage III and bears a poor prognosis with a global 1 and 5-year survival of 32 to 64% and 3 to 23% for stages IIIA and IIIB, respectively. Radiotherapy has been the cornerstone of treatment of this presentation of lung cancer. Sixty gray of irradiation delivered continuously by daily fractions in 6 weeks is presently considered as minimal standard of local therapy. Current research focuses on optimization of radiotherapy delivery taking into account assessment of tumor motion, precision of tumor volume definition, and better understanding of radiation dose distribution/delivery (e.g., 3D conformal radiotherapy and intensity modulated radiotherapy). Local relapse and distant failure leading eventually to death in a large number of patients are nevertheless highly indicative of suboptimal treatment. The optimal treatment strategy for these patients remains to be defined. The American Society of Clinical Oncology guidelines recommend combined modality treatment with platinum-based chemotherapy and definitive thoracic radiation particularly for patients with good performance status. Randomized studies and a recent meta-analysis suggest that concurrent chemoradiotherapy leads to a superior outcome compared with sequential treatment at the expense of increased local toxicity. Whereas platinum-based doublets remain the standard regimen, the choice, and addition of a third complementary agent is the subject of investigation. In the setting of stage IIIB–IV NSCLC, no clear or only marginal differences exist between platinum-based doublets and triplets. However, addition of gemcitabine to a platinum doublet was shown marginally superior in a meta-analysis compared with a platinum doublet including a first or second generation drug without gemcitabine. Furthermore, the ad-
dation of gemcitabine to the carboplatin-paclitaxel doublet was demonstrated to be safe and to result in a significantly superior treatment outcome in a phase II to III study in advanced NSCLC compared with carboplatin-paclitaxel alone.10 In operable NSCLC, the cis- or carboplatin-containing triplet combinations used as induction chemotherapy (including paclitaxel and gemcitabine) before surgery were shown superior to doublet combinations in individual non-randomized studies.11

The assumption of potentially increased antitumor efficacy of the triplet and its safety constituted the rationale for combining the paclitaxel, carboplatin, and gemcitabine (PACCAGE) regimen with radiotherapy in a sequential program delivering the chemotherapy first followed by consolidation radiotherapy in patients with inoperable NSCLC. Phase II results (efficacy and toxicity) of the chemotherapy part (PACCAGE) were recently published on 48 patients.12 Here, we report the final analysis of the total cohort of 64 patients included in the study, their response and long-term outcome.

PATIENTS AND METHODS

Patients from a single institution older than 18 years with histologically or cytologically confirmed NSCLC, clinical stage IIIA or stage IIIB (without malignant pleural effusion), Karnofsky Performance Score of 80 to 100, who were not candidates for surgery, did not undergo previous radiotherapy or chemotherapy or did not suffer from a previous cancer (except for basocellular epitheloma of the skin or in situ cancer of the cervix assumed to be cured with a follow-up of more than 5 years), and signed informed consent were enrolled from January 4, 2001 till January 10, 2005. Patients were staged clinically and those with enlarged mediastinal lymph nodes visualized on computerised axial tomography (CT) scan and with positive spots on 18fluoro-deoxy-glucose (18FDG)—positron emission tomography (PET) scan were considered inoperable according to the institutional surgical guidelines and eligible for the study. Those who underwent a thoracotomy after a negative mediastinoscopy and were judged inoperable according to the institutional surgical guidelines and eligible for the study. Ineligibility included patients with T4 tumors invading the vertebral body or supraclavicular lymph nodes, presence of atelectasis of the whole lung, and a tumor of the superior sulcus. Standard eligibility criteria for chemotherapy included adequate blood chemistry, normal bone marrow, hepatic and renal function, and absence of severe pulmonary or cardiovascular disease. Eligibility for induction chemotherapy followed by radiotherapy was assessed during a multidisciplinary consultation in the presence of a medical oncologist and a radiotherapist.

Assessment Procedures

Pretreatment evaluation included patient history, physical examination, performance status, standard chest x-ray, complete blood chemistry and blood count, CT scan of the chest and abdomen, bone scintigraphy, fiberoptic bronchoscopy plus biopsy, 18FDG-PET-scan, and any other clinical or radiologic procedure deemed necessary to rule out metastatic disease. Mediastinoscopy was performed only in otherwise surgical candidates. These examinations were performed within 4 weeks of the first administration of chemotherapy. A complete blood count and clinical examination was performed weekly (days 1, 8, and 15 of a 3-week cycle) during chemotherapy. Complete blood chemistry was performed on day 1 of each new cycle. A complete clinical and radiologic reevaluation using the same imaging techniques as before chemotherapy was performed before radiotherapy (within 3–4 weeks after the last chemotherapy administration in cycle 3) and 1 to 2 month after completion of radiotherapy. The possibility to repeat the examinations earlier was an option for patients with a suspicion of progressive disease before scheduled reevaluation. During follow-up, a clinical examination, a hematological, and biochemical blood evaluation and a CT scan of the thorax was mandatory every 3, 4, and 6 months in the first 2 years in years 3 and 4 and year 5 and beyond, respectively. The clinical response to induction chemotherapy and to radiotherapy was assessed using CT scan according to the World Health Organisation criteria.13 Objective response rate (OR) was defined as the sum of the complete plus partial response (PR) rate. In a subgroup of patients, 18FDG-PET scan was added after induction chemotherapy in parallel with CT scan but not always repeated after radiotherapy. Response on 18FDG-PET was defined according to the completeness of the resolution of enhanced 18FDG uptake in the tumor as detailed previously.14 All patients accrued into the study were included in the final analysis.

Treatment Delivery

Chemotherapy

On day 1 of each chemotherapy cycle, paclitaxel (175 mg/m2 by 3-hour infusion on day 1) preceded the administration of carboplatin (AUC 5 mg/ml. min by IV bolus) and gemcitabine (1000 mg/m2 by IV bolus). On day 8, gemcitabine (1000 mg/m2 by IV bolus) was repeated. On day 1 of each cycle premedication consisted of ondansetron (8 mg IV bolus), dexamethasone (20 mg IV bolus), promethasine (50 mg s.c.), and ranitidine (300 mg IV bolus), all administered 30 minutes before paclitaxel. Oral ondansetron was administered if necessary after day 1. On day 8, 50 mg of alizapride by IV bolus was given 30 minutes before gemcitabine and continued orally if necessary afterward.

Dose Reductions of Chemotherapy. Doses were reduced according to hematological and nonhematological NCI-CTC version 2.0 toxicity criteria.15 No dose reescalation was allowed if a dose had to be reduced previously. The details of the guidelines and procedures of dose reductions on days 1 and 8 of each cycle according to hematological and nonhematological toxicity were published before.12

Radiotherapy

Radiotherapy was initiated at least 4 weeks after completion and recovery from induction chemotherapy toxicity. For radiotherapy planning purposes, patients underwent “slow” CT (Somatom +, Siemens, Erlangen, Germany) in supine position. Image sets were constructed, with and without iodine contrast enhancement (100 mL of Telebrix-35β).
Delineation and dose computation were performed on the GRATIS planning system implemented on a Unix work station (Ultra-2, Sunsparc). Whenever available, images of the diagnostic \( ^{18} \)FDG-PET were used for planning purposes. They were imported in the delineation console to allow for proper fusion using Syntegra in stead of coregistration. Final delineation was performed on the “a blanc” CT series. Using \( W = 1600 \) and \( L = -300 \) for the parenchyma, and \( W = 400 \) and \( L = 800 \) for the mediastinum. The contrast series was useful in adjusting the delineation, but it could not be used for dose computation. The \( ^{18} \)FDG-PET data were used to distinguish tumor from atelectasis or to locate mediastinal lymph node involvement when not visible on CT. The following target volumes were defined: gross tumor volume (GTV) primary, GTV lymph nodes (all lymph nodes with a short axis of \( >1 \) cm, lymph nodes \( <1 \) cm when clustered), clinical target volume (CTV) primary (a 5-mm three-dimensional expansion around the GTV primary in the parenchyma or mediastinum, with exclusion of mediastinal vessels, bone, heart or esophagus, unless diagnostic imaging revealed a \( T_3 \)-stage due to invasion in the previously mentioned structures), and CTV nodes (all lymph node regions in which GTV nodes were defined, based on either CT imaging. \( ^{18} \)FDG-PET, histologic or cytologic evidence or combination of these). Delineation of the entire attained lymph node region according to the Naruke classification was performed to obtain the CTV nodes, however, without elective nodal irradiation. Planning tumor volume (PTV) margins were 5 or 8 mm for primary tumors in either upper or middle/lower lobe location, respectively. PTV expansion on CTV nodes was 3 mm. Three-dimensional, coplanar, conformal beam setup was used for planning purposes using up to six beam incidences. The plan objective was to deliver 66 Gy in 2 Gy fractions to the entire PTV according to ICRU guidelines, without violation to the normal dose constraints. Dose constraints for organs at risk were set as follows: maximal dose to the spinal cord of 53 Gy in 30 fractions, the volume receiving 20 Gy of the entire lung minus GTV (V20) below 30% and the mean lung dose below 17 Gy, less than one third of the esophagus could receive 66 Gy, and less than half 35 Gy. In case of conflict between PTV coverage and dose to the spinal cord or lungs, priority was given to the organ at risk and dose was lowered to 60 Gy. Patients showing evidence of progressive disease at any site were excluded from high dose radiotherapy and were treated with palliative intent when indicated. Dose schedules varied depending on the presence of extra thoracic disease, the tumor volume, and the general condition of the patient.

Acute and late lung toxicity was scored using the RTOG/EORTC morbidity scoring classification. Radiologic changes were evaluated by two physicians independently on repeated CT scans. Changes in pulmonary function tests (PFTs) were categorized using the SOMA/LENT scale, primarily evaluating the 1 second forced expiratory volume (FEV1) and lung diffusion capacity for carbon monoxide (DLCO). \( ^{16} \)

### Supportive Treatments

- Growth factors (filgrastim, recombinant human erythropoietin), transfusions (red blood cells, platelets), antibiotics, and other supportive drugs or measures during induction chemotherapy were used when necessary. Dose delays and reductions were recommended rather than the use of secondary prophylaxis for neutropenia with filgrastim.

### Statistical Analysis

The study was initially conceived as a phase II study of triplet induction chemotherapy (before consolidation radiotherapy) in stage III unresectable NSCLC. To reject an acceptable OR of \( \leq 45\% \), 31 eligible patients had to be accrued in the study. \( ^{17} \) After the demonstration of an OR of \( >45\% \) and the feasibility to deliver full-dose radiotherapy in the first cohort of patients, an amendment was approved to include a unspecified additional number of patients. All analyses were performed according to the intention-to-treat (ITT) principle.

Confidence limits (95\% CI) of response rate were estimated according to Simon. \( ^{18} \) Time to progression and time to survival were defined as the period from the first day of treatment to the date of first evidence of disease progression and/or death or to loss of follow-up, respectively. Survival estimates were generated using the method of Kaplan and Meier. \( ^{19} \) To study the potential influence of major baseline characteristics (stage of disease, age, sex, histology, and PS) on survival, a uni- and multivariate analysis according to the Cox logistic regression model was performed. \( ^{20} \)

### RESULTS

#### Patient Characteristics

A total of 64 patients were enrolled in this study, and disease characteristics are detailed in Table 1. Twenty patients presented with \( T_1 \) and 25 with \( T_4 \) tumors. The patients with \( T_1,6 \) and \( T_2,13 \) tumors were classified in the stage IIIA or stage IIIB category based on the mediastinal nodal status (N2 or N3). Only three of the patients included were inoperable after exploratory thoracotomy. In the remaining 61 patients, inoperability was decided upon clinical staging. A comparative analysis of outcome with \( ^{18} \)FDG-PET and CT response before and after induction chemotherapy was possible in 31 patients. \( ^{14} \) Assessment of the overall treatment response (chemotherapy and radiotherapy) was possible in 47 patients.

### Treatment Delivery

#### Induction Chemotherapy

All but one patient received at least one cycle of chemotherapy. One female patient developed a grade 3 ana-

<table>
<thead>
<tr>
<th>TABLE 1. Patient Characteristics</th>
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<tbody>
<tr>
<td>Number</td>
</tr>
<tr>
<td>Median age, yr (range)</td>
</tr>
<tr>
<td>Male/female (%)</td>
</tr>
<tr>
<td>Stage IIIA/IIIB (%)</td>
</tr>
<tr>
<td>Karnofsky Performance Score 100-90-80 (%)</td>
</tr>
<tr>
<td>Histology (%)</td>
</tr>
<tr>
<td>Squamous cell cancer</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
</tr>
<tr>
<td>Large cell carcinoma</td>
</tr>
<tr>
<td>Undefined</td>
</tr>
</tbody>
</table>
Toxicity Grade 3 (%) Grade 4 (%)

Toxicity of Chemotherapy

TABLE 2. Toxicity of Chemotherapy

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Grade 3 (%)</th>
<th>Grade 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucopenia</td>
<td>20 (31.3)</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>22 (34.4)</td>
<td>23 (35.9)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>14 (21.9)</td>
<td>6 (9.4)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (3.1)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Infection</td>
<td>2 (3.1)</td>
<td>1 (1.6)</td>
</tr>
<tr>
<td>Nonhematological</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>4 (6.2)</td>
<td>0</td>
</tr>
<tr>
<td>Arthralgia/myalgia</td>
<td>5 (7.8)</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (4.7)</td>
<td>0</td>
</tr>
<tr>
<td>Polyneuropathy</td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Rash</td>
<td>2 (3.1)</td>
<td>0</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (1.6)</td>
<td>0</td>
</tr>
<tr>
<td>Nonthrombocopenic hemoptyis</td>
<td>0 (0)</td>
<td>1 (1.6)</td>
</tr>
</tbody>
</table>

Values are presented as n (%); n = 64.

Salvage Systemic Therapy

On completion of consolidation radiotherapy, only 13 of 50 relapsing patients received salvage second or further-line systemic treatment. This consisted mainly of single agent therapy with vinorelbine, docetaxel, gemcitabine, pemetrexed, or a tyrosine kinase inhibitor. Four patients received a tyrosine kinase inhibitor as only salvage therapy. With salvage chemotherapy only three disease stabilizations with short duration were observed (2 as the second line and 1 as the third-line chemotherapy). The number of patients with stage IIIA or stage IIIB receiving no salvage systemic therapy was identical: 13 of 19 (68%) and 24/35 (69%) in stages IIIA and IIIB, respectively.

Radiotherapy

Radiotherapy was initiated 41 days (median value) after completion of induction chemotherapy. Delivery of full-dose radiotherapy was achieved within a median number of 45 days.

A full radiotherapy “dose equivalent” of 66 Gy on the primary tumor and lymph nodes was delivered in 47 patients (73%). The dose of radiotherapy was reduced to <45 Gy in 11 patients (17%). In five of them, this was because of development of metastases and in three because of local progression during radiotherapy. In additional three patients, the dose was reduced for technical reasons (tumor volume). No radiotherapy was delivered in six patients (10%), in five because of demise before radiotherapy could be initiated: one patient died during the first cycle of chemotherapy due to PD, two patients died during chemotherapy due to tumor-related events in the absence of progressive disease and two patients died between chemo- and radiotherapy. One patient underwent surgery after induction chemotherapy and appeared to be a pathologic complete responder.

Toxicity of Radiotherapy

Acute

One patient died within 4 weeks after the end of radiotherapy with the acute respiratory distress syndrome. Autopsy revealed a combined effect of radiation pneumonitis, tumor progression, and infection. In all patients, a grade \( \leq 3 \) acute esophagitis lasting for 2 to 4 weeks was observed.
Late
No grade 3 or more late esophageal toxicity could be reported. Late lung toxicity measured in changes in PFTs was acceptable. In more than half of the patients the change in PFTs when compared with the baseline value was less than 25%. Only 7% of patients experienced a decline of more than 50% (Soma-Lent criteria). Lung toxicity based on the RTOG-EORTC criteria showed radiologic changes in 80% of patients with a patchy dense pneumonitis in six patients. Adding the clinical data, the incidence of grade 3 radiation pneumonitis rose to 18%. Overall, late lung toxicity included a grade 2 SOMA-LENT and a grade 3 RTOG/EORTC toxicity in 44% and 18% of the patients, respectively (Figures 1A, B).

Response
Induction Chemotherapy
The response rate of the ITT population was 55% (Table 3). In the category “Not Evaluables” (NE) for response, five patients did not receive the planned three cycles because of toxicity (three patients) or early death (two patients). Only four patients developed progressive disease under chemotherapy and they received one (two patients), two (one patient), or three cycles (one patient) of chemotherapy. The single patient (stage IIIB) who underwent “curative” surgery in stead of radiotherapy after completion of induction chemotherapy is reported under PR.

Overall Treatment Effect
Of the 64 patients constituting the ITT study population only 47 patients (40 received a full-dose radiotherapy and seven a reduced dose) had comparative CT scans before and 1 to 2 months after completion of radiotherapy. The average calculated remaining tumor surface in these 47 patients after induction chemotherapy was 41% (range 6–122%). After the consolidation radiotherapy, this was further reduced to a calculated surface of 29% or a total reduction of 71%. This finding suggested a larger tumor “shrinkage” with chemotherapy than with consolidation radiotherapy (−59% versus −29% relative reduction, respectively). Respectively, 30 and 17 of these 47 patients achieved a PR (64%) and minor response or stable disease (36%) after induction chemotherapy. All of the 30 patients with a PR after induction chemotherapy remained in PR after consolidation radiotherapy, whereas 10 of 17 patients with minor response or stable disease after induction chemotherapy were converted into PR.

Survival Parameters
Time to Progression
With a median follow-up of patients alive of 59.1 month (range 39.2–82.4 month), the median time to progression of the ITT population was 10.9 month (95% CI: 7.9–13.5 month) (Figure 2A). Stage IIIA patients achieved a significantly longer time to progression compared with stage IIIB patients (15 versus 8.7 month; \( p = 0.049 \)).

Eight of the 64 patients included are alive without clinical or radiologic evidence of relapse at time of the most recent evaluation (December 15, 2008). Fifty-six patients have died of whom six with no relation to tumor relapse and four with unknown reasons. In 46 patients, the pattern of initial relapse could be documented: local relapse only in 18, metastatic only in 10, and a combination of local relapse plus metastases in 18. In nine patients initial relapse was in the brain, in six as the only site. No specific histologic subtype predisposing for brain metastasis was found in this series.

Survival
The median survival of the ITT population was 17.2 month (95% CI: 12.8–22.6 month) with a significant differ-

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**TABLE 3. Radiological Response After Induction Chemotherapy**

<table>
<thead>
<tr>
<th></th>
<th>CR</th>
<th>PR</th>
<th>SD</th>
<th>PD</th>
<th>NEa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IIIA (n = 25)</td>
<td>0</td>
<td>18</td>
<td>5</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Stage IIIB (n = 39)</td>
<td></td>
<td>16</td>
<td>15</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>All (n = 64)</td>
<td>1</td>
<td>34</td>
<td>20</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

* Not evaluable: early death: 2 (pneumonia cycle 1, hemoptisis cycle 2); gastrointestinal toxicity GR 3: 2 (cycle 1 and 2); anaphylaxis to P GR 3: 1 (cycle 1).

**a** \( p = \) (Fisher’s exact test).

CR, complete response; PR, partial response; SD, stable disease; NE, not evaluable; PD, progressive disease; CI, confidence interval.
The median survival of 17.2 months obtained overlaps with the median survival reported in the four randomized studies of sequential versus concomitant chemoradiotherapy (16.5 month, range 16.3–17.0 month).3–6 In our stage IIIA patients, a survival of 17.5% at 5 year is observed. This seems similar to the results of the concomitant chemoradiotherapy rather than the sequential arms in the randomized studies (16%, 21%, and 19% 5-year survival for Furuse et al., Fournel et al., and Zatloukal et al., respectively).3,5,6 Thirty-nine percentage of our patients presented with stage IIIA quite comparable with 44%, 33%, and 15% of patients with stage IIIA enrolled in the concurrent arms of the randomized studies, respectively.3,5,6 The favorable results obtained in our stage IIIA population could also be explained by the potential selection bias of more “low volume” disease in our stage IIIA cohort. No clear explanation is available for the poor median survival of 10.5 month in the present stage IIIB patient cohort compared with a previously published 10.8 months with an analogous chemotherapy regimen in ap-

FIGURE 2. A, B, time to progression (A) and overall survival (B). Full line represents the total population, dotted line represents stage IIIA dashed line represents and stage IIIB patients.

ence between stage IIIA and stage IIIB patients (23.4 versus 10.5 month; p = 0.011) (Figure 2B). An update of the survival data in patients evaluated through 18FDG-PET demonstrated that patients with a metabolic complete response (mCR) lived significantly longer than those without mCR (49 versus 14 month p < 0.005), which corroborated the previously published results.14 The number of patients that underwent a repeat assessment with 18FDG-PET after radiotherapy was too small to allow any further analysis on the potential impact of the consolidation radiotherapy. The % 5-year survival was 12.5% overall, favoring stage IIIA patients (17.5% and 6.4% in stages IIIA and IIIB, respectively).

In the subset of 47 patients in whom a CT scan was available before induction chemotherapy and after consolidation radiotherapy, a reduction of ≥80% of the initial tumor surface on CT was predictive for a longer median time to progression (11 versus 18.6 month; p = 0.0117) but only a trend for survival was observed (15.7 versus 31.1 month; p = 0.111).

DISCUSSION

We have demonstrated that the use of induction chemotherapy with three cycles of PACCAGE before consolidation radiotherapy is safe and active in patients with stage III NSCLC. These results are in line with earlier data using the same chemotherapy in stages IIIB to IV NSCLC.21–23 Expanding the number of patients from 48 in our previous report to the total of 64 included in the trial did not alter the toxicity nor activity results significantly. The OR obtained in the present report was 55%, slightly less than in the previous one (62.5%).12 Of notice is the superior response in stage IIIA (72%) versus IIIB (46%) patients indicating a higher activity of chemotherapy with lower tumor burden. In the study by Abratt et al. and Giannotti et al.,11,24 81.5% and 72.7% OR was obtained after three cycles of an identical regimen before surgery in 29 stage IIIA (out of a total of 44) and 52 bulky stage IIIB patients, respectively. Although OR was high in these studies, a pathologic complete responder was rather exceptional (five and four patients, respectively). The fact that the antitumor activity of the PACCAGE regimen correlates with stage and/or volume of disease is also illustrated by the comparison of the three other studies.21–23 In the first study that included 90% of stage IV patients, the overall OR was 26%.21 In the second study 73% of the patients were stage IV and the OR increased to 44%.23 Finally in the third study, 28 of 41 patients included were in stage III and the OR in these patients was 68%.22

Mainly nonhematological toxicity and early tumor-related events was the reason for early termination of chemotherapy in eight patients in our study. Nevertheless, hematological toxicity may have been underestimated in the present study because of the mandatory dose reductions and as a consequence of the potential underreporting of hematological toxicity on day 15 during cycles 2 and 3 (not all patients had blood counts done on day 15 of cycles 2 and 3). Fifty-six patients (91%) were, however, able to complete the intended three cycles, some at a reduced dose.

We were also able to show that standard full-dose radiotherapy could be delivered in time in 73% of the patients with acceptable toxicity. The reasons for not being able to deliver the full dose were in the majority of cases not radiotherapy, but rather tumor—or patient related. Nevertheless, apart from the well known and transient esophageal toxicity, lethal acute pulmonary toxicity in combination with infection and local tumor progression was observed in one patient only. The late pulmonary toxicity grade 3 was similarly acceptable and comparable with other sequential chemoradiation regimens.25 Although no direct comparison is possible with concurrent chemoradiotherapy, acute and late toxicity seems to favor our sequential approach.7

The median survival of 17.2 months obtained overlaps with the median survival reported in the four randomized studies of sequential versus concomitant chemoradiotherapy (16.5 month, range 16.3–17.0 month).3–6 In our stage IIIA patients, a survival of 17.5% at 5 year is observed. This seems similar to the results of the concomitant chemoradiotherapy rather than the sequential arms in the randomized studies (16%, 21%, and 19% 5-year survival for Furuse et al., Fournel et al., and Zatloukal et al., respectively).3,5,6 Thirty-nine percentage of our patients presented with stage IIIA quite comparable with 44%, 33%, and 15% of patients with stage IIIA enrolled in the concurrent arms of the randomized studies, respectively.3,5,6 The favorable results obtained in our stage IIIA population could also be explained by the potential selection bias of more “low volume” disease in our stage IIIA cohort. No clear explanation is available for the poor median survival of 10.5 month in the present stage IIIB patient cohort compared with a previously published 10.8 months with an analogous chemotherapy regimen in ap-
paren tally far more advanced “wet” stage IIIIB and IV disease.\textsuperscript{10} Indirect proof of a selection of a poor prognostic group of stage IIIIB patients in the present study may be suggested by the large number of patients failing to complete the full treatment program including the induction chemotherapy and the consolidation radiotherapy part in stage IIIIB (23 of 39) (data not shown).

Treatment failure in locally advanced NSCLC includes local and metastatic relapse in most of patients.\textsuperscript{2} In the present study around 50\% or more of the patients with long-term follow-up presented with local and metastatic relapse. Improved radiotherapy and better systemic treatments need therefore to be developed. Our observations\textsuperscript{14,16} and those of others\textsuperscript{26} about the predictive power of a local mCR by \textsuperscript{18}FDG-PET and a long-term survival after induction treatment is suggestive for using this tool to guide the consolidation radiotherapy. Especially those patients, not achieving a mCR after induction chemotherapy are potentially at high risk for first local relapse and should be offered higher radiotherapy doses (e.g., via intensity-modulated Radiotherapy) or be the subject of research aimed at improving local control. Furthermore, better systemic treatments are needed to achieve better local and systemic effects.

The high incidence of first relapse in the brain, with six patients of 64 developing them as the only site in our study should receive special attention. A baseline magnetic resonance imaging scan of the brain may therefore be useful before the start of induction chemotherapy and before consolidation radiotherapy in the absence of any clinical central nervous system symptomatology. This may avoid the unnecessary morbidity of chemother- and radiotherapy administered with curative intent. These data support prophylactic cranial irradiation (PCI) in selected patients such as adenocarcinoma, a minority in our population, that have a high propensity for the development of brain metastases and more specifically those patients that have a high probability of long-term survival predicted by a mCR. One small randomized study demonstrated a significant reduction in the incidence of brain metastasis in patients with operable stage IIIA NSCLC undergoing PCI added to induction chemotherapy and concomitant chemoradiotherapy followed by surgery versus no PCI. The neurocognitive functioning was preserved in that study.\textsuperscript{27}

In conclusion, we have shown that induction chemotherapy adding gemcitabine to the doublet consisting of carboplatinum and paclitaxel followed by standard consolidation radiotherapy is active and feasible in stage III inoperable NSCLC. Whether the novel triplet is superior to the currently used doublets as induction chemotherapy (in terms of clinical activity, toxicity, outcome, and economical cost) or achieves long-term results compared with concomitant chemoradiotherapy should be evaluated in a randomized trial.

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