Induction chemotherapy with cisplatin and gemcitabine followed by concurrent chemoradiation with twice-weekly gemcitabine in unresectable stage III non-small cell lung cancer: Final results of a phase II study

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1. Introduction

Approximately 30% of patients with non-small cell lung cancer (NSCLC) present with locally advanced disease. Some of these patients can benefit from a surgical approach [1,2], but the great majority of patients with stage IIIb, and many with stage IILa (e.g. N-2 bulky) are not eligible for surgery. It is presently accepted that the best treatment for these patients is the combination of chemotherapy and radiotherapy. Some comparative clinical studies [3—5] show that concurrent chemoradiotherapy (CCR) is more effective than sequential treatment, though at the expense of a major nonhematological toxicity (mainly esophagitis and pneumonitis).

Despite these new therapeutic approaches, the results remain poor, with 3-year survival below 20%. Two possible strategies are available to improve this situation. First, the incorporation of induction or adjuvant chemotherapy to concurrent treatment, as represented in the studies CALGB-9431 and SWOG 9504, respectively [6,7]. The second strategy consists of using more radiosensitive drugs, such as gemcitabine, in concurrent chemoradiotherapy.

The optimal dose for the administration of gemcitabine combined with radiotherapy has been evaluated in various phase I trials [8—11]. In these studies, the recommended weekly dose of gemcitabine concurrent to radiotherapy was between 100 and 375 mg/m², depending on the dose of radiotherapy, the type of planning (2D or 3D), and the volume of treatment. In the first phase II trial published, gemcitabine was administered at full weekly doses of 1 g/m² during six consecutive weeks, combined with 60 Gy of thoracic radiation [12]. High levels of toxicity were observed, resulting in serious esophagitis and pneumonitis, with three toxic deaths in the eight patients included. Other phase II studies were subsequently published, based on the results of the phase I trials mentioned, obtaining mean survival of about 15 months [13—15].

In addition, we must mention the phase II randomized trial carried out by CALGB [6], comparing three classical combinations of chemotherapy (cisplatin—gemcitabine, cisplatin—vinorelbine and cisplatin—paclitaxel) concurrent to radiotherapy. In the gemcitabine arm, after two cycles of induction, radiotherapy was combined with the administration of cisplatin 80 mg/m² every 3 weeks, and gemcitabine 600 mg/m² on days 1 and 8 of each cycle. Esophagitis grades III and IV was observed in 52% of cases. Overall response and survival were similar in the three treatment arms.

Nevertheless, experiments in vitro showed that gemcitabine radio sensitization did not exceed 72 h. Thus, twice-weekly administration of gemcitabine would seem an attractive schedule [16]. Using this scheme, Blackstock presented the preliminary results of a phase I trial in ASTRO 1999 [17].

On the basis of these results, the Associació Catalana per a la Recerca Oncològica i les seves implicacions Sanitàries i Socials (ACROSS) undertook a phase II study to evaluate the efficacy and toxicity of a radiotherapy treatment concomitant with gemcitabine administered twice-weekly, in patients with locally advanced and unresectable NSCLC, followign induction chemotherapy with cisplatin and gemcitabine.

2. Methods

This was a multicentric, non-randomized phase II study. The institutional ethics committees of each participating center approved the study protocol.
2.1. Eligibility criteria

Eligible patients had histologic or cytologic documentation of NSCLC and unresectable or inoperable stage III disease. Patients with malignant pleural effusion were ineligible. Patients with non-extirpable locoregional recurrence of tumors previously resected were also enrolled. All patients presented at least one lesion measurable in two-dimensions, by computed tomography (CT), or magnetic resonance (MR) performed within 28 days of registration. Additional eligibility criteria included Karnofsky index equal or superior to 70%, age of 18 years or older, and absence of pregnancy. Required initial laboratory tests included an absolute granulocyte count of \( \geq 1500 \, \mu L^{-1} \), hemoglobin \( \geq 10.5 \, g/dL \), platelet count of \( \geq 100,000 \, cells/\mu L \), and creatinine clearance of at least 55 mL/min. In addition, liver function tests has to be \( \leq 1.5 \) times the upper limit of normality, and the forced expiratory volume in 1 s has to over 1000 mL. Eligible patients had no serious medical illnesses preceding treatment and no other primary invasive cancer unless they had been disease-free for at least 5 years.

All patients were visited by a radiation oncologist before registration in the study. Determination of PTV was required, and patients were only eligible if this parameter was under 2200 cm³, in accordance with the scheme proposed by CALGB/ROTG [18]. Written informed consent was obtained from each patient prior to study entry.

2.2. Initial evaluation

Baseline evaluation was performed within 28 days before treatment and included a complete medical history and physical examination, complete blood cell count, blood chemistry studies, flexible bronchoscopy, electrocardiography, pulmonary function test including lung diffusion capacity for carbon monoxide, chest radiography, and computed tomography of the chest and abdomen. CT or MR imaging of the brain and bone scintigraphy were not mandatory in absence of symptoms.

2.3. Study design

This was a multicentric, non-randomized phase II trial. The initial design of the study contemplated the administration of induction chemotherapy with 3 cycles of cisplatin and gemcitabine at a dose of 100 mg/m² on day 1 and 1250 mg/m² on days 1 and 8, respectively. Following response assessment, and in the absence of progression, radiotherapy was initiated with concurrent gemcitabine administered twice-weekly (50 mg/m² Mondays and Thursdays).

The results obtained for the first 22 patients (group A) showed an excessive level of nonhematological toxicity. Subsequently, the dose of cisplatin was reduced to 70 mg/m², and gemcitabine dose during concurrence was adjusted to 35 mg/m² for the following 34 patients included (group B).

Concurrent radiotherapy with gemcitabine was initiated between the third and fourth week after the third cycle of chemotherapy. High-energy photons (6–23 MeV) produced in a lineal accelerator were used. Planned dose was 68.4 Gy, and fractionation was standard. Radiotherapy was delivered in two phases. During the first phase of the treatment, 45 Gy was administered with opposed anterior and posterior fields. In the second phase, macroscopic disease was overdosed to 68.4 Gy, with a minimum of 2 entry fields. The maximum dose permitted on the spinal cord was 45 Gy and efforts were made to include less than 16 cm of esophagus. Dose fractionation was according to the definitions of ICRU 50 and ICRU 62 [19]. All patients received elective nodal irradiation. PTV included, with a margin of 1.5 cm, the primary tumor, homolateral hilum and mediastinum. In cases of N3 involvement, contralateral hilum was irradiated. Homolateral supraclavicular fossa was only treated in upper-lobe tumors or in supraclavicular N3 (in this case, both supraclavicular fossas were treated). 3D planning system was used in 2 of the 3 centers where radiotherapy was administered, and dose-volume histograms were used to calculate PTV. In the third centre, PTV was calculated from transversal tomographic slices every 25 mm. PTV was deduced from the interpolation of reference isodose.

Rules were established to adjust cytostatics dose throughout induction chemotherapy, as well as during CCR, according to hematological toxicity. Treatment was discontinued when esophagitis or pneumonitis reached grade II or over. It was resumed when these were resolved, reducing the dose of gemcitabine 50%. If toxicity was not resolved after 2 weeks, the patient was excluded from the study.

2.4. Study evaluation and statistical methods

Primary endpoints of this phase II trial were response to complete treatment and toxicity observed during CCR. Secondary endpoints included response and toxicity to induction treatment, time to progression, overall survival and locoregional control rate.

Although response rate to induction chemotherapy was not the main aim of our study, it was used to calculate sample size, as its assessment required the greatest number of patients. We considered the hypothesis of obtaining at least 30% response to induction chemotherapy, with a possible maximum of 50%. Using the Fleming method, sample size was calculated in 60 patients, for an alpha value of 5%, a power of the study of 80%, and a possible loss of follow-up of 15%.

We reduced cisplatin dose during induction and gemcitabine dose during concurrence, as a result of the detected toxicity. However, the trial was not designed to compare the efficacy and toxicity of two levels of doses. Thus, a comparative statistic analysis between the two groups was not carried out, although the results are presented separately.

The safety analysis included all patients who received at least one dose of chemotherapy. Common Toxicity Criteria scale was used for toxicity assessment, except in lung and esophageal toxicity derived from CCR, for which the RTOG and RTOG/EORTC criteria were used.

All eligible patients at study entry were included in the population for efficacy, in terms of response, survival and time to progression. Patients evaluable for response to induction and complete treatment included
all the patients who had received at least one cycle of cisplatin–gemcitabine. Responses to induction and complete treatment were assessed separately with a CT scan after each phase. After completion of treatment, bimonthly follow-up chest radiographs were performed and CT scans were repeated every 6 months.

Overall survival and time to progression was determined on the basis of the method of Kaplan and Meier [20].

3. Results

3.1. Patient characteristics

Fifty-six patients were included in 8 centers between April 2000 and April 2003: 22 were included before the previously described dose reduction (group A), and 34 after (group B). One patient in group B was not eligible for efficacy analysis as PTV volumes obtained were above acceptable levels. He was nevertheless included in the toxicity analysis, as he had received one cycle of induction.

Table 1 summarizes patients’ characteristics: all the patients included except one were males. 46 patients (82.1%) had stage IIIb disease, defined by T4 in the majority of patients (44 cases, 78.6%). N-0, N-2 and N-3 categories were described in 37.5, 33.9 and 19.6% of the patients, respectively. No patient had N-1 disease. The most frequent histology was squamous carcinoma (55.3%). Most patients (76.7%) presented a basal Karnofsky index of 80—90%. Mean age was 61.5 years, and PTV ranged from 700 to 2200 cm$^3$ (mean: 1580 cm$^3$).

3.2. Compliance to treatment

In group A, 40.9% of patients completed planned treatment, compared to 57.5% in group B. The overall percentage was 50.9% for all patients. Table 2 shows patients’ compliance to treatment and causes for interruption.

Eleven of the 55 eligible patients (5 in group A and 6 in group B) were withdrawn from the study during induction. Causes included: toxicity in 2 cases (grade III thrombopenia and cisplatin-related acute tubular necrosis), adverse event in 2 cases (tuberculosis and pulmonary thromboembolism), progression of disease (3 cases), early death (1 case), and patient/investigator’s request (3 cases). Sixteen patients abandoned the study during concurrent (8 in group A and 8 in group B). Reasons included: toxicity to treatment (10 cases), progression of neoplasia (2 cases), adverse event (1 case: pulmonary thromboembolism), protocol violation (1 case), and patient/investigator’s request (2 cases). Thus, the most frequent cause for interruption of treatment was toxicity of CCR in both groups (esophagitis and pneumonitis grade III unresolved in 2 weeks).

Of the 44 patients who initiated CCR, 9/17 (52.3%) in group A and 17/27 (62.9%) in group B completed planned treatment. However, the proportion of patients who — after starting radiotherapy — received a minimum of 60 Gy was similar in the two groups (70.5 and 70.3%, respectively).

3.3. Toxicity

Patients’ toxicities during induction and CCR (grades III—IV) are shown in Tables 3 and 4. During induction, the main difference between the two groups was a higher incidence of vomiting and grades III and IV neutropenia in group A. Likewise, Karnofsky index evolution was assessed in 21 patients of group A and in 24 patients of group B. Karnofsky index worsened in 47.6% of cases in group A, and 25% in group B.

During concurrent treatment, higher levels of hematological toxicity were detected in group A. A high incidence of esophagitis and radiation pneumonitis was observed in both groups, despite the reduction of the dose of gemcitabine in group B. Finally, 17.6% of grades III and IV radiation dermatitis was detected in the patients who received 50 mg/m$^2$ of gemcitabine.

Four toxic deaths occurred during the study, three in group A and one in group B; all were due to radiation pneumonitis.

3.4. Response

Responses to induction and complete treatment were analyzed separately in the two groups. These results are resumed in Table 5. Response to induction could not be analyzed in five patients: two patients were not evaluable as they did not complete a whole cycle of chemotherapy; one patient was withdrawn from the study due to thrombopenia and response assessment was not made; one patient abandoned the study, and the fifth patient was diagnosed of pulmonary tuberculosis, and response assessment was not performed satisfactorily. Likewise, response to complete treatment could not be assessed in seven
Table 2  Compliance to treatment<sup>a</sup>

<table>
<thead>
<tr>
<th></th>
<th>Group A</th>
<th>Group B</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients who initiated induction</td>
<td>22</td>
<td>33</td>
<td>55</td>
</tr>
<tr>
<td>Interruption during induction</td>
<td>5 (22.7%)</td>
<td>6 (18.1%)</td>
<td>11 (20%)</td>
</tr>
<tr>
<td>Causes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Adverse event (not toxicity)</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Death</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Patient/investigator’s request</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Progression</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Patients who initiated concurrence</td>
<td>17</td>
<td>27</td>
<td>44</td>
</tr>
<tr>
<td>Interruption during concurrence</td>
<td>8 (47.0%)</td>
<td>8 (29.6%)</td>
<td>16 (36.3%)</td>
</tr>
<tr>
<td>Causes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxicity</td>
<td>4</td>
<td>6</td>
<td>10</td>
</tr>
<tr>
<td>Adverse event (not toxicity)</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Patient/investigator’s request</td>
<td>2</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Progression</td>
<td>1</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Transgression of protocol</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Treatment completed</td>
<td>9 (40.9%)</td>
<td>19 (57.5%)</td>
<td>28 (50.9%)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Only eligible patients.

Table 3  Toxicity of induction (only grades III and IV)

<table>
<thead>
<tr>
<th>Toxicty</th>
<th>Group A (22 patients)</th>
<th>Group B (34 patients)</th>
<th>Total (56 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 30</td>
<td>1 3.1</td>
<td>7 13.5</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>6 30</td>
<td>6 18.8</td>
<td>12 23.1</td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>2 10</td>
<td>2 6.2</td>
<td>4 7.7</td>
</tr>
<tr>
<td>Anaemia</td>
<td>— —</td>
<td>1 3.1</td>
<td>1 2.3</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1 5</td>
<td>1 3.1</td>
<td>2 3.8</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 5</td>
<td>1 3.1</td>
<td>2 3.8</td>
</tr>
<tr>
<td>Anorexia</td>
<td>— —</td>
<td>1 3.1</td>
<td>1 1.9</td>
</tr>
<tr>
<td>Pruritus</td>
<td>— —</td>
<td>1 3.1</td>
<td>1 1.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>— —</td>
<td>1 3.1</td>
<td>1 1.9</td>
</tr>
<tr>
<td>Transaminases</td>
<td>— —</td>
<td>1 3.1</td>
<td>1 1.9</td>
</tr>
</tbody>
</table>

Table 4  Toxicity of concurrence (only grades III—V)

<table>
<thead>
<tr>
<th>Toxicty</th>
<th>Group A (17 patients)</th>
<th>Group B (27 patients)</th>
<th>Total (44 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n %</td>
<td>n %</td>
<td>n %</td>
<td></td>
</tr>
<tr>
<td>Anaemia</td>
<td>1 5.8</td>
<td>— —</td>
<td>1 2.2</td>
</tr>
<tr>
<td>Thrombopenia</td>
<td>6 35.2</td>
<td>1 3.7</td>
<td>7 15.9</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>4 23.5</td>
<td>— —</td>
<td>4 8.8</td>
</tr>
<tr>
<td>Infection</td>
<td>1 5.8</td>
<td>— —</td>
<td>1 2.2</td>
</tr>
<tr>
<td>Esophagitis</td>
<td>6 35.2</td>
<td>9 33.3</td>
<td>15 34.0</td>
</tr>
<tr>
<td>Radiation pneumonitis</td>
<td>4 23.5</td>
<td>7 25.9</td>
<td>11 25</td>
</tr>
<tr>
<td>Radiation dermatitis</td>
<td>3 17.6</td>
<td>1 3.7</td>
<td>4 8.8</td>
</tr>
<tr>
<td>Thromboembolic accidents</td>
<td>2 11.7</td>
<td>— —</td>
<td>2 4.4</td>
</tr>
<tr>
<td>Hemolytic-uremic syndrome</td>
<td>1 5.8</td>
<td>— —</td>
<td>1 2.2</td>
</tr>
</tbody>
</table>
patients (the five aforementioned plus one patient in each group who died after finalizing concurrence before response assessment). In short, global response rate to induction treatment was 50 and 48.4% for groups A and B. Global response rate to complete treatment was 68.1% for group A and 63.6% for group B. Overall global response was 49.1% for induction treatment and 65.4% for complete treatment.

3.5. Time to progression and survival assessment

With a mean follow-up of 41.2 months, median time elapsed from treatment initiation to the first progression was 9.8 months in group A and 10.7 months in group B.

Mean survival was 11.3 months for group A (95% CI 5.7–19.0) and 21.5 months for group B (CI 95% 9.5–27.6). Overall mean survival was 17.7 months (95% CI 9.5–24.3). Three-year survival for the whole group of patients was 20%. Figs. 1 and 2 represent progression-free and global survival in groups A and B and in the whole population.

3.6. Sites of first failure

Information about the first progression was not available in 19 cases. All these patients were prematurely withdrawn from the study because of early death, toxicity, adverse event or patient/investigator’s request. Progression was not observed in 5 of the 55 patients eligible (9.1%). Information about the site of first progression was obtained in the remaining 31 patients. Twenty-three different locations were described, lung and bone being the most frequent. First progression was metastatic spread alone in 13 of these 31 patients. Thus, local control was achieved in 18/55 patients (32.7%). In the remaining 18 patients locoregional relapse was demonstrated, with or without synchronous metastasis. In five patients, first relapse was dissemination in the central nervous system.

3.7. Evaluation of response and radiological follow-up

A poor correlation between radiological and clinical outcome of the cases was persistent throughout the study: many patients underwent radiological assessment of disease persistence, or even progression, while a favorable clinical evolution was evidenced (Fig. 3). However, this correlation
was not systematically analyzed, as it was not contemplated in the original design of the study.

4. Discussion

In our study, we analyzed the efficacy and toxicity of concomitant radiotherapy with gemcitabine administered at low doses twice a week, in patients with locally advanced unresectable NSCLC, following three cycles of induction chemotherapy with cisplatin and gemcitabine. Our results are encouraging with regard to efficacy objectives: response rate and global and progression-free survival. However, the nonhematological toxicity detected, though not very different from that communicated in other concurrence studies, remains excessive.

Global response rate to complete treatment (65%) is comparable to that communicated in other larger trials [6,7]. Nevertheless, radiological assessment of response may not be a good method to assess the real efficacy of this type of treatment, as will be discussed further. The response rate to induction treatment (50% for group A and 48.4% for group B) confirmed our hypothesis when designing the study. We must point out the similarity of these two percentages, despite the reduction of the dose of gemcitabine. Esophagitis was the most frequent cause for treatment interruption. However, we must point out the high prevalence of esophagitis in other studies that explore concurrence: 17% in SWOG/9504 [7]; 52, 39, and 25% in the gemcitabine, paclitaxel and vinorelbine arms of CALGB/9431 [6].

The risk factors for developing esophagitis were analyzed in a retrospective study of 215 patients with locally advanced lung cancer treated with CCR and 3D planning [22]. In this report, the incidence of esophagitis grade III or IV was 20.5%. The predictive factors of developing this toxicity were the median dose administered to the esophagus, and the parameters related to the volume of esophagus irradiated.

Although esophagitis was the main cause for treatment interruption in our study, radiation pneumonitis was the most frightening toxicity. It caused four deaths in our study. In several cases, pneumonitis did not lead to an interruption of treatment, as it appeared during the first or second month of follow-up. Several predictive factors have been published for the development of pneumonitis in patients treated with concomitant CCR. These factors could be divided in two groups: patient-dependent factors, and those dependent on the technique of radiotherapy used. Amongst the patient-related factors, Robnett et al. describe a low-performance status, female sex and FEV1 < 2 L [23]. Other authors have also mentioned a higher risk in patients with chronic obstructive pulmonary disease [24,25]. Likewise, a Japanese study [26] relates the apparition of pneumonitis with the serum levels of KL-6, an antibody against human lung adenocarcinoma. Regarding risk factors related to the technique of radiotherapy or dosimetric aspects, we can mention the irradiation of the lower lung lobes [27,28], the mean dose of radiotherapy administered in the lungs [24,29,30], the irradiation of contralateral mediastinum [31], and the V-20 or percentage of pulmonary volume irradiated with more than 20 Gy [24,32,33]. The risk of pneumonitis grade II or superior seems to be 8–18% in patients with a V-20 over 20%.

Ever-improving knowledge of these factors and continuous progress in planning techniques and administration of radiotherapy will allow the reduction of toxicities in CCR.

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Fig. 2  (A) Overall survival of groups A and B. Mean survival— group A: 11.3 months; group B: 21.5 months. (B) Global overall survival. Mean survival: 17.7 months.
treatments, particularly regarding nonhematological toxicities. In the last few years, not only has 3D planning become imperative, but PET-CT has also been introduced as an increasingly accessible tool for an optimal definition of the volumes to irradiate. There is an evident need to adjust radiotherapy fields to the macroscopic tumor, avoiding elective radiation of the mediastinum. Moreover, in the next years, the use of new 4D treatment planning techniques (gating and tracking), will allow further reduction of such toxicities and improve long-term results of the treatment.

Finally, we wish to reflect about the validity of conventional image techniques in the assessment response and in the follow-up of patients with locally advanced lung cancer treated with schemes of CCR. In our experience, the use of CT in this context had limited usefulness in many cases, due to the important fibrotic alterations observed post-treatment. Outcome of neoplastic disease could only be adequately interpreted by clinical follow-up of patients, as is illustrated in Fig. 3. Other authors have looked into this topic more extensively [34,35]. Thus, median survival and the percentage of survival at 3 and 5 years emerge as the most credible and definitive parameters of efficacy, that are communicated uniformly in this type of studies, even in phase II trials. Some authors have studied the role of PET or PET-CT in the early assessment of response to CR and their results seem to have a better correlation with patients’ survival [36,37].

In conclusion, concomitant radiotherapy administered twice a week with low-dose gemcitabine, following induction chemotherapy with three cycles of cisplatin and gemcitabine, produces an interesting response rate and median survival for patients with locally advanced unresectable NSCLC. Nevertheless, the striking nonhematological toxicities of this scheme are disappointing. Likewise, radiological follow-up is very difficult in these patients, due to the important fibrotic sequelae of CR.

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Conflict of interest: The authors disclose any financial and personal relationship with other people or organisation that could inappropriately influence the study.

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