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Phase I study of pemetrexed and cisplatin with concurrent high-dose thoracic radiation after induction chemotherapy in patients with unresectable locally advanced non-small cell lung cancer

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ABSTRACT

Purpose: This is a phase I, escalating-dose trial targeting exclusively patients with non-small cell lung cancer (NSCLC), investigating pemetrexed and fixed-dose cisplatin concurrently administered with high-dose radiotherapy (RT) after induction chemotherapy (CT). Primary objective was to determine the maximum tolerated dose and recommended phase II dose of pemetrexed.
Patients and Materials: Patients with unresected stage III NSCLC, planned V20 ≤ 35%, and FEV ≥ 1.3 L, were treated every 21 days for 2 cycles (pemetrexed 500 mg/m^2; cisplatin 75 mg/m^2), followed by 2 cycles of concurrent CT-RT: pemetrexed starting dose was 400 mg/m^2, escalated up to 800 mg/m^2 per 100 mg/m^2 dose level (DL), cisplatin at 75 mg/m^2 and RT at fixed dose of 66 Gy/33 fractions.
Results: Nine of 10 enrolled patients (age range 46–68 years; 6 men; ECOG PS 0 [6 patients], PS 1 [4]; stage IIIA [1], IIIB [9]; 6 adenocarcinomas, 3 squamous cell carcinomas, 1 large cell carcinoma) were entered on 3 DLs. Dose escalation of pemetrexed was conducted up to 600 mg/m^2 based on the independent safety monitoring board recommendation. One dose-limiting toxicity occurred at DL3: Grade 4 septic shock. Grade 3 related toxicities: 2 neutropenia at DL3, 2 lymphopenia per DL (3 recurrent), 2 leukopenia (1 recurrent) at DL3, 1 gastric pain (DL3), 1 nausea and 1 recurrent vomiting (DL2). No Grade 3/4 radiation-related toxicities were observed. No toxic death was observed. Disease control rate was 77.7% (1 CR, 4 PR, 2 SD). One-year survival rate was 90%.
Conclusions: This phase I report of pemetrexed is dedicated to NSCLC with induction therapy and fixed high-dose RT. Pemetrexed at 500 mg/m^2, concurrently given with cisplatin and RT was well tolerated and appears to be the only third-generation agent that can likely be recommended safely at full dose in future trials with concurrent RT.

1. Introduction

It is estimated that 30–40% of patients with a locally advanced non-small cell lung cancer (NSCLC) are potentially eligible for curative chemoradiation (CT-RT). A statistically significant overall survival improvement in favor of the concurrent combination (HR = 0.84; $p = 0.004$) was reported compared to the sequential combination with a higher relative risk of Grade 3/4 acute esophagitis (RR = 4.9; $p < 0.001$) [1]. However, the optimal strategy remains undefined, leading to a major clinical challenge of distant control as no third-generation agent can be given at full systemic dose when combined with thoracic radiation [2]. The addition of induction or consolidation chemotherapy may limit micro-metastatic disease; in terms of efficacy and safety both strategies are feasible.

Given the absence of any proven benefit in favor of one strategy versus the other, we opted for an induction design considering that it may offer some advantages: extra time to plan for radiotherapy, selection of the more appropriate patient for local treatment, and reduction of tumor size (smaller radiation volume and higher radiotherapy dose) [3,4].

Pemetrexed (Alimta®), a multitargeted folate inhibitor within the larger class of antimetabolite chemotherapies, has an evident activity in metastatic NSCLC in first-, second-line, and maintenance setting [3,5]. Seiwert et al. [6] evaluated pemetrexed, a potent

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radiosensitizer, with radiotherapy in a phase I, dose-escalation, multitumor study in patients with locally advanced and metastatic NSCLC or esophageal cancer. Patients were treated every 21 days for two cycles. Regimen 1 was pemetrexed (200–600 mg/m^2); regimen 2 included pemetrexed (500 mg/m^2) with escalating carboplatin doses (area under the curve [AUC] 4–6). Both regimens included concurrent radiation (40–66 grays (Gy). Dose escalation was discontinued when pemetrexed 600 mg/m^2 was reached for regimen 1. Therefore, 500 mg/m^2 was recommended in regimen 2. Both regimens were well tolerated and the maximum tolerated dose (MTD) was not reached. Two dose-limiting toxicities (DLT), Grade 4 and 3 esophagitis, occurred at dose level (DL) 500 mg/m^2 of regimen 1 and DL 500 mg/m^2 with carboplatin AUC 6 of regimen 2, respectively [6].

Based on these findings, we conducted a prospective, multicenter, single-arm, open-label phase I study to assess the concurrent combination of pemetrexed with a fixed cisplatin dose and a high fixed dose of thoracic radiotherapy after induction chemotherapy, exclusively in patients with unresected stage IIIA/B NSCLC. The primary objective was to determine the MTD of pemetrexed and the phase II recommended dose.

2. Patients and methods

2.1. Patient eligibility

The protocol was approved by the National Ethics Committee of Lyon (France). All patients provided written informed consent before enrolment in the study. Patients between 18 and 70 years with a histologically or cytologically proven unresected stage IIIA/B NSCLC (TNM 6th edition, Mountain et al., 1997) were eligible; no pleural/pericardial effusions; at least one measurable lesion meeting Response Evaluation Criteria in Solid Tumors (RECIST, Therasse et al., 2000); Eastern Oncology Cooperative Group (ECOG) performance status (PS) 0 to 1; Forced Expiratory Volume in one second (FEV_1) $\geq$ 1.3 L; total lung V20 $\leq$ 35%; adequate hematological and liver functions; calculated creatinine clearance $\geq$45 mL/min. Exclusion criteria included invasive malignancy within the past 5 years (except in situ cervix carcinoma, non-melanoma skin cancer or treated low grade localized prostate cancers, post-resection intrathoracic tumor recurrence or prior chemotherapy for NSCLC), pregnancy, ongoing breast-feeding, unwillingness to use adequate contraception during study therapy; inability to interrupt nonsteroidal anti-inflammatory therapy; inability or unwillingness to take folic acid, vitamin B12, or dexamethasone. Weight loss was not an exclusion criterion.

2.2. Treatment plan

Physical examination, ECOG PS evaluation, complete blood count, chemistry, and body surface area calculation were performed at baseline and before each cycle of chemotherapy. Treatment plan is presented in Fig. 1.

All patients received vitamin supplementation and steroids. Oral daily folic acid (0.4 mg) 5–7 days prior to pemetrexed initiation, continuing daily until 3 weeks after the last dose of pemetrexed. Vitamin B12 (1 mg intramuscularly) was started 1–2 weeks prior to pemetrexed initiation and every 9 weeks until 3 weeks after the last pemetrexed dose.

All patients received 2 cycles of induction pemetrexed and cisplatin. Concurrent CT-RT treatment was initiated 4 weeks after the last induction chemotherapy infusion in patients with PS 0-1, disease control, and without Grade $\geq$2 toxicities.

The starting cohort received pemetrexed at 400 mg/m^2 on Day 1 of a 21-day cycle and protocol-designed increments were 100 mg/m^2 up to 800 mg/m^2 with concurrent fixed dose of cisplatin. The maximum treatment duration was 12 weeks; follow-up was 12 months after the end of radiotherapy.

Patients underwent CT-based simulation at baseline and post-induction visit and were treated with 3-dimensional conformal radiotherapy at a total dose of 66 Gy/33 fractions, 5 days/week over 7 weeks. Radiotherapy treatment volumes were defined based on pretreatment chest computed tomography scan. The gross tumor volume (GTV) included clinically macroscopic disease on imaging modalities: including the primary tumor (GTV-T) and abnormally enlarged regional lymph nodes >1.0 cm short axis measurement (GTV-N). A clinical target volume (CTV) included subclinical spread of the disease around the GTV. An expansion of 1 cm from GTV to CTV was performed for each patient. Elective node irradiation was not allowed. The planning target volume (PTV) included an internal margin to account for respiratory motion and a set-up margin to compensate set-up errors. A total expansion of 1.0–2.0 cm from CTV to PTV was performed according with tumor location and histology. Most of the time, the PTV to block edge expansion was around 5 mm, depending on the characteristics and measurements for each machine.

Normal tissues were contoured in their entirety including lungs, external contours, heart, spinal cord, esophagus, and liver, with the following constraints: no more than 35% of total lung volume could receive a dose exceeding 20 Gy (V20). When planning the beam arrangement to the PTV, the heart, esophagus, and spinal cord had to be out of the field to the extent possible.

2.3. Toxicity and response assessment

Toxicity was evaluated according to the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTC-AE), version 3. Acute and late radiation side effects were reported using the Radiation Therapy Oncology Group (RTOG) Acute and Late Radiation Morbidity Scoring criteria, respectively. Late RTOG toxicities were defined as those occurring 90 days after the start of radiotherapy. Each patient was followed for 1 year after the end of the treatment.

Tumor assessment was performed by investigators using RECIST. Restaging scans were performed 23–28 days after the last induction chemotherapy, at the 1-, 3-, 6-, and 9-month follow-up visit after the last dose of radiotherapy.

2.4. Dose escalation

Dose escalation is described in Fig. 1. DLT was defined as Grade 4 neutropenia >7 days; Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding; any Grade 3 nonhematological toxicity >5 days (including febrile neutropenia) or any Grade 4 toxicity, except nausea, vomiting, and alopecia; any radiation toxicity Grade 3/4 and death due to toxicity, occurring during the radiation period, including 4 weeks recovery.

Three patients were to be entered per DL. If no DLT occurred, 3 patients were to be entered at the next DL. If 1 DLT occurred, 3 additional patients were to be entered at the same dose level. MTD was defined as the dose inducing DLT to at least 2 of 3 patients or 2 of 6 patients. The recommended phase II dose was the dose of the level preceding the MTD level.

2.5. Statistical considerations

Patients receiving at least 1 cycle of concomitant CT-RT were included in the primary endpoint and efficacy analysis. Patients receiving at least 1 dose of pemetrexed or cisplatin (including induction therapy) were evaluated for other safety parameters.