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Original Research

Induction or consolidation chemotherapy for unresectable stage III non-small-cell lung cancer patients treated with concurrent chemoradiation: a randomised phase II trial GFPC – IFCT 02-01☆

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Abstract ***Purpose:*** The objective of this randomised phase II study was to evaluate the impact in terms of response and toxicities of induction or consolidation chemotherapy respectively before or after concurrent chemoradiotherapy in unresectable stage III non-small-cell lung cancer.
Patients and methods: In the induction arm, patients received induction chemotherapy with cisplatin (80 mg/m^2) and paclitaxel (200 mg/m^2) on days 1 and 29 followed by a concurrent chemoradiotherapy (66 Gy in 33 fractions, cisplatin 80 mg/m^2 days 1, 29 and 57, vinorelbine 15 mg/m^2 days 1, 8, 29, 36, 57 and 64). In consolidation arm, the same concurrent chemoradiotherapy began on day 1 followed by two cycles of cisplatin and paclitaxel.
Results: One hundred twenty seven patients were randomised. The intent to treat response rates in induction and consolidation arms were 58% and 56% respectively. Median survival was 19.6 months in induction arm and 16.3 months in consolidation arm and 4-year survival rates were 21% and 30% respectively. Haematologic and non-haematologic toxicities were similar in both arms, except grade 3/4 oesophagitis, more frequent in consolidation arm than in induction arm (17% versus 10%).
Conclusion: Cisplatin-based chemotherapy as induction or consolidation with concurrent chemoradiotherapy can be administrated safely. Response rates were similar in both arms with a trend in favour for consolidation arm for long-term survival.

1. Introduction

About 30% of patients with non-small-cell lung cancer (NSCLC) have unresectable stage III disease at diagnosis. The current standard of care of these patients is concurrent treatment with platinum-based chemotherapy and thoracic radiotherapy [1–3]. Randomised clinical trials and meta-analyses have generally shown trends in favour of combination chemoradiotherapy compared with radiotherapy alone, as well as concomitant compared with sequential chemoradiotherapy [4–8]. While the data available provide general support for concurrent chemoradiotherapy, many important questions remain [9]. The combination of agents, the total dose delivered and the schedule of administration must all be considered in order to optimise the management of these patients and there are currently insufficient data in these areas [9].

The combination of third generation cytotoxic drugs and thoracic radiotherapy often needs a dose-reduction of chemotherapy due to increase of radiation therapy toxicity. Full dose chemotherapy before (induction chemotherapy) or after (consolidation chemotherapy) the concurrent chemoradiotherapy may help to eradicate the metastatic component of disease. The optimal sequencing between chemoradiotherapy and chemotherapy is still not well defined [8,9].

We decided to explore both induction and consolidation strategies in a randomised phase II setting. The objective was to evaluate the impact in terms of response and toxicities of both strategies using cisplatin-paclitaxel as induction or consolidation chemotherapy and cisplatin-vinorelbine during radiotherapy. We chose cisplatin-vinorelbine doublet for its good efficacy/toxicity profile when associated to thoracic radiotherapy [10–13]; cisplatin-paclitaxel doublet, tested in a large randomised phase III trial in stage IV NSCLC, showed a good response rate (28%) and a better overall survival (OS) compared to carboplatin/paclitaxel ($p = .019$) [14] and can be so considered as a good induction or consolidation chemotherapy. On the other hand, the use of docetaxel was proposed in this setting [15,16] but at the time of our study design, docetaxel was not approved in first line chemotherapy for advanced NSCLC by French health regulatory authorities.

2. Patients and methods

2.1. Eligibility criteria

The main inclusion criteria were: histogical proven NSCLC, unresectable stage IIIAN2 or stage IIIB without pleural involvement or supra-clavicular lymph nodes invasion, at least one measurable target, Eastern Cooperative Oncology Group score 0 or 1, weight loss less than 10%, age between 18 and 70 years, normal hepatic, renal and haematologic functions, with haemoglobin ≥9.5 g/dl, satisfactory respiratory function ($FEV_1 > 40\%$ of theoretical value and $PaO_2 > 60$ mmHg) and written informed consent. The main exclusion criteria were active uncontrolled infection, unstable cardio-vascular disease, peripheral neuropathy grade 1 or more, psychiatric or neurologic disorders, previous malignancy (except for in situ carcinoma of the cervix, basocellular skin cancer). Pre treatment assessment included laboratory test parameters, chest X-ray, bronchoscopy, chest and brain computed tomography (CT) scan, abdominal CT scan,