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Dose escalation to 84 Gy with concurrent chemotherapy in stage III NSCLC appears excessively toxic: Results from a prematurely terminated randomized phase II trial

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ABSTRACT

Objectives: Concurrent chemoradiotherapy is the mainstay treatment for NSCLC stage III disease. To investigate whether radiation dose escalation based on individual normal tissue constraints can improve outcome, the Swedish lung cancer study group launched this randomized phase II trial.

Materials and Methods: NSCLC patients with stage III disease, good performance status (0–1) and adequate lung function (FEV1 > 1.0 L and CO diffusion capacity > 40%) received three cycles of cisplatin (75 mg/m^2 day 1) and vinorelbine (25 mg/m^2 day 1 and 8) every third week. Radiotherapy started concurrently with the second cycle, with either 2 Gy daily, 5 days a week, to 68 Gy (A) or escalated therapy (B) based on constraints to the spinal cord, esophagus and lungs up to 84 Gy by adding an extra fraction of 2 Gy per week.

Results: A pre-planned safety analysis revealed excessive toxicity and decreased survival in the escalated arm, and the study was stopped. Thirty-six patients were included during 2011–2013 (56% male, 78% with adenocarcinoma, 64% with PS 0 and 53% with stage IIIB). The median progression-free survival (PFS) and overall survival (OS) were 11 and 17 months in arm B compared to the encouraging results of 28 and 45 months in the standard arm. The 1- and 3-year survival rates were 56% and 33% (B) and 72% and 56% (A), respectively. There were seven toxicity-related deaths due to esophageal perforations and pneumonitis: five in the escalated group and two with standard treatment.

Conclusion: Dose-escalated concurrent chemoradiotherapy to 84 Gy to primary tumor and nodal disease is hazardous, with a high risk of excessive toxicity, whereas modern standard dose chemoradiotherapy with proper staging given in the control arm shows a promising outcome with a median survival of 45 months and a 3-year survival of 56% (NCT01664663).

1. Introduction

The treatment development over the last decades for patients with NSCLC stage III disease has been disappointing despite numerous attempts to improve outcome. Strategies including addition of maintenance therapy (e.g. docetaxel), addition of targeted therapy (e.g. cetuximab) and introduction of newer chemotherapy agents such as pemetrexed or tumor vaccines all failed to increase survival beyond that provided by the presiding concept of concurrent chemoradiotherapy. A platinum-based chemotherapy doublet combined with radiation doses to 60 Gy, or somewhat higher, is still considered standard therapy in most clinics. The successive improvement in survival over the years reported in different trials addressing the stage III population is probably primarily attributable to a more precise staging with PET/CT, imaging of the brain, and invasive approaches with EBUS and EUS and thereby enabling more accurate patient selection. The majority,

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however, still relapse with distant metastases and a substantial proportion with locoregional recurrence. To counteract the latter and hopefully also impact distant metastases by the thoracic sterilization of tumor cells, a number of trials in early 2000 investigated dose-escalated radiotherapy. Rosenman et al. [1] showed that it was possible to give 74 Gy in a concurrent manner without reaching the maximum tolerable dose (MTD), and Socinsky et al. performed a trial with concurrent chemoradiotherapy to 90 Gy [2]. Bradley et al. escalated the radiation doses in a feasible manner to > 80 Gy if V_{20} was < 25% [3], and Belderbos et al. also reached > 80 Gy in stage III patients when taking the mean lung dose (MLD) into account [4]; noticeably, the last two trials were without concurrent chemotherapy. Individual dose escalation based on constraints were also studied, e.g. reaching 79.2 Gy delivered with 1.8 Gy BID without excessive toxicity, in this particular study with sequential chemotherapy [5].

As feasibility with dose escalation had been shown in several one-armed trials, the Swedish lung cancer study group strived to investigate concurrent chemoradiotherapy with dose escalation based on individual tissue constraints in a randomized manner with comparison to a standard treatment arm to be able to obtain a signal of treatment efficacy. The study was designed as a randomized open phase II trial, and in 2011 the PLANET trial (Phase II randomized study on locally advanced NSCLC, escalated dose on individual basis, treatment with radiochemotherapy) was launched.

2. Patients and methods

2.1. Objectives and trial design

The main objective was to explore the hypothesis that a higher radiation dose based on individual normal tissue constraints would improve time to progression or death, with progression-free survival (PFS) as the primary endpoint. Secondary endpoints were overall survival, toxicity according to NCI-CTCAE version 4.0, local control, relapse pattern and health-related quality of life (HRQL) measured with EORTC QLQ 30 and LC14. The trial was designed as an open label, parallel group phase II trial assigned to the group by block randomization with a block size of four in a 1:1 ratio. The trial was approved by the ethics board in Gothenburg, Sweden, and conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines as defined by the International Conference on Harmonization. A written informed consent was collected from all the patients before they were enrolled by the participating investigators, and the trial was registered at www.clinicaltrials.gov (NCT01664663).

2.2. Patient eligibility

Patients were eligible if they had a histological or cytological diagnosis of non-resectable NSCLC stage IIIA/IIIB (TNM 7th edition), no prior chemotherapy or radiation therapy for NSCLC, WHO performance status of 0–1, FEV1 ≥ 1.0 L and CO diffusion capacity (DLCO) > 40%, adequate bone marrow reserve and were > 18 years of age. Main exclusion criteria were excessive weight loss within six months (> 10%), supraclavicular nodes, apical tumors (“Pancoast tumors”), inadequate liver or kidney function, serious other concomitant systemic disorders or second primary malignancy. Pre-study assessments included a CT scan of the thorax and abdomen, a PET/CT and a CT scan or MRI of the brain not older than four weeks by the time of inclusion. Invasive staging was not mandatory but was performed at the discretion of the investigator. In addition, all patients went through spirometry and an electrocardiography as well as baseline assessments with regard to HRQL and toxicity.

2.3. Treatment schedule and radiotherapy details

The treatment schedule consisted of three cycles of cisplatin (75 mg/m^2) on day 1 and vinorelbine (25 mg/m^2) i.v. on day 1 and 8 given i.v. every third week. Cisplatin could, after the first cycle, be replaced by carboplatin in case of decline of renal function or hearing loss. Radiotherapy was initiated concurrent with the second cycle, and the patients were prepared by a CT scan in the treatment position immobilized in vacuum pillows. Dose planning based on four-dimensional CT (4DCT) and an additional PET/CT were optional. The gross tumor volume (GTV) was delineated with the surrounding subclinical extension (approximately 1 cm) encompassing the clinical target volume (CTV). An additional margin for organ and patient movements and inaccuracies in beam and patient setup constituted the planning target volume (PTV), which usually varied between 0.5–1.0 cm depending on whether a 4DCT approach was used. The radiation was delivered by 3DCRT planning or VMAT/IMRT techniques with 2 Gy per fraction, five days a week. In the standard arm (A), patients received one fraction a day to a total dose of 68 Gy, with a total treatment time of 6.5 weeks. In the experimental arm (B), the dose was escalated to the whole CTV (i.e. primary tumor and involved nodes), depending on individual dose constraints, by adding an additional fraction per week (with at least 6 h between fractions) to a maximum of 84 Gy delivered within the same total treatment time. The constraints taken into account upon dose escalation were for the spinal canal 50 Gy, and for lung tissue two levels were used depending on the CO diffusion capacity; if CO diff. cap. > 60%, no more than 50% of the normal total lung volume should receive a dose above 20 Gy (V_{20} < 50%), and if the CO diff. cap. was 40–60%, the V_{20} should be < 35%. The esophageal constraint was initially a mean dose of < 45 Gy, with a later high dose constraint added in an amendment where the maximum dose encompassing the total circumference as per CT slice had to be below 74 Gy, and a maximum of 30% of the circumference was allowed to receive a dose of 78 Gy. The organs at risk (OAR) priority was as follows: spinal cord > lung > esophagus. If the doses exceeded the constraint levels in the escalated arm, it was allowed to decrease the dose to smaller areas within the PTV to a minimum of 95% of 68 Gy (64.6 Gy) giving some dose heterogeneity, or second, shrink the PTV margins involved if it could be done without compromising the doses to the CTV. In a third step, the dose was decreased by 2 Gy at a time until the OAR doses were below constraint levels.

2.4. Follow- up

The patients were followed during therapy with toxicity scoring, blood chemistry and performance status assessments at least every third week. After therapy, they were clinically assessed at six weeks and underwent radiological evaluations (CT) according to RECIST 1.1 every third month the first year, followed by every sixth month thereafter. PET/CT and spirometry were performed at six months after therapy. HRQL was measured at baseline, at one week after treatment, at three months and at 12 months after completion of therapy. The patient data were continuously collected at the participating sites.

2.5. Statistics

The trial was designed as a randomized phase II trial with PFS as the primary endpoint. Based on our previous trials in the same stage III population [6,7], we estimated an improvement in PFS from 20% at two years in the standard arm to 40% in the dose-escalated arm. With a power of 80% and a two-tailed significance level of 5%, 116 patients (58 in each arm) were necessary to detect such a difference. The assumption was that patients were to be enrolled for three years and that the analysis should be performed after three years of follow-up. The method in use is based on a comparison of two exponential survival functions with a parametric test of the hazard between the groups. To account for possible incorrect inclusions and other unintended violations, five extra subjects per arm were added to a total sample size of 126 patients. A safety analysis was pre-planned after the inclusion of 30