Lung Cancer 69 (2010) 218–224

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

First-line cisplatin with docetaxel or vinorelbine in patients with advanced non-small-cell lung cancer: A quality of life directed phase II randomized trial of Gruppo Oncologico Italia Meridionale

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ARTICLE INFO

Article history:
Received 24 March 2009
Received in revised form 6 October 2009
Accepted 9 October 2009

Keywords:
Quality of life
Chemotherapy
Non-small-cell lung cancer
Vinorelbine
Docetaxel

ABSTRACT

Background: Quality of life (QoL) has gained greater importance in the management of metastatic non-small-cell lung cancer due to the palliative nature of treatment. Docetaxel (DCT) and cisplatin (CDDP) doublet has been reported to be associated to a better QoL than the weekly vinorelbine (VNR) and CDDP regimen. Recently a newer more tolerated schedule of the VNR/CDDP regimen has been published and is widely employed in medical practice. The impact of these regimens on patients' QoL as well as symptoms control and type and grading chemo-related side-effects has been compared prospectically.
Methods: Patients received CDDP 75 mg/m^2 plus DCT 75 mg/m^2 on day 1 every weeks (arm A) or CDDP 80 mg/m^2 on day 1 plus VNR 30 mg/m^2 day 1 and 8 every 3 weeks (arm B). G-CSF and/or EPO were employed as needed. Health-related QoL was assessed at entry and after every cycle by the EORTC-QLQ-C30 and LC13 questionnaires, toxicity by the NCI-NCCN CTC vs 2, and intent-to-treat objective response by the Recist criteria.
Results: The QoL questionnaires were completed by 37 pts (88%) in the DCT/CDDP arm and 39 pts (87%) in the VNR/CDDP one. Baseline mean scores and rates at which pts failed to complete QoL assessment were similar in the two arms. Global health status of the EORTC QLQ-C30 scale and specific symptoms control (LC13 module) improved during treatment without any statistically significant difference between the two arms. Emotional functioning remained stable in both groups during treatment, whereas physical and role improved slightly. In the DCT/CDDP arm 14 pts (33%; 95%CL 24–40%) had PR, and 10 (24%) SD for a 57% TGCR. In the VNR/CDDP arm 12 pts (27%) achieved PR, 18 (41%) SD a 68% TGCR. Differences were not statistically significant. Median time-to-progression was 4.2 months in the DCT/CDDP arm and 4.5 months in the VNR/CDDP one, and median overall survival was 12.1 (range 1–26+ months) and 12.5 months (range 1–28+ months) for DCT/CDDP and VNR/CDDP arms, respectively. Febrile neutropenia rate was higher in the VNR/CDDP arm ($p = 0.02$) as well as G3-4 anemia ($p = 0.005$) and G-CSF/EPO use ($p = 0.019$).
Conclusions: Global and specific health-related QoL data similar in both treatment groups with no statistically significant difference. Efficacy measures, overall response rate, time-to-progression and overall survival were equivalent in both arms. However, severe anemia and febrile neutropenia are statistically more frequent in the VNR/CDDP arm than in the DCT/CDDP one. These data should be considered in treatment decision-making for pts with advanced non-small-cell lung cancer and for the design of future trials with chemotherapy plus biologics.

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doi:10.1016/j.lungcan.2009.10.008

1. Introduction

Despite considerable progress achieved in the last two decades advanced non-small-cell lung cancer (ANSCLC) still remains a challenging neoplastic disease beyond the possibility of cure for the vast majority of patients [1,2]. Even when the newer chemotherapeutic and biologic agents are optimally employed in combination median survival of selected patients in clinical trials do not exceed a median of 12 months [3–5]. Moreover the activity of third-generation doublet regimens has reached a plateau. Most regimens produce very similar results so that therapeutic choice should be based on expected toxicity, familiarity with a certain combination, convenience of administration, and costs [6,7]. Therefore, although for clinical investigators and regulatory purposes, overall survival is generally the most important measurement of efficacy of any antineoplastic treatment, evaluation of quality of life (QoL) and cancer-related symptoms control rate have gained considerable importance for patients, their caregivers and oncologists dedicated to the management of thoracic malignances [8,9].

Cancer chemotherapy can both positively and negatively affect QoL since tumor response can have a positive impact on survival and QoL while side-effects can have a negative impact on these parameters. To date most regulatory agencies recognize that end points other than survival may be important in evaluating the efficacy of new oncology products to the point that relief of tumor-specific symptoms provided support for the USA Food and Drug Administration approval of 23% of the 57 oncology drug approvals between 1990 and 2002 [8,9]. Moreover QoL at baseline may be of greater prognostic value than disease stage or performance status in ANSCLC and patients reported outcomes might be considered for stratification purposes in future trials [10,11]. Further studies are needed to determine whether interventions that improve patients reported outcomes also increase survival and to identify explanatory mechanisms through which they may relate to survival.

Among third-generation regimens the combination of weekly vinorelbine (VNR) and cisplatin (CDDP) has been reported to be active but frequently associated with severe hematological toxicity, which may impair patients QoL [12,13]. This observation has been reported in prospectively randomized studies comparing weekly VNR/CDDP to other active regimens such as docetaxel (DCT) plus CDDP or gemcitabine plus CDDP. However, the weekly regimen has been modified employing a more tolerated schedule, which has been shown to retain the same efficacy of the weekly VNR regimen [14–16]. The VNR/CDDP regimen has been successfully employed in combination with cetuximab in ANSCLC and is also considered the standard adjuvant treatment for high-risk patients with radically resected NSCLC [4,17,18].

In this paper we report the results of a randomized phase II study comparing the modified VNR/CDDP regimen to the DCT/CDDP one primarily in terms of quality of life, symptoms control and toxicity profile.

2. Patients and methods

2.1. Patient selection

Patients were recruited from 11 oncology centers in Southern Italy belonging to the Gruppo Oncologico Italia Meridionale (GOIM, protocol n. 2608). Eligible patients were those with histologically confirmed advanced NSCLC including patients with loco-regionally advanced unresectable non-metastatic stage IIIB disease (only N3 supraclavicular or T4 for pleural effusion) or metastatic stage IV tumor according to the revised International Staging System. Patients had also to include the following inclusion criteria: age between 18 and 70 years, no prior chemotherapy, at least one site of measurable disease accordingly to the RECIST criteria [19], an Eastern Cooperative Oncology Group performance status <2, weight loss <5% within the last 3 months,white blood cell count $\geq$3,500/μL, neutrophils $\geq$1,500/μL, platelets $\geq$100,000/μL, hemoglobin $\geq$9.0 g/dL, serum creatinine $\leq$1.5 mg/dL, the creatinine clearance should be >60 mL/min, bilirubin $\leq$1.2 mg/dL, and AST, and ALT within 2 times the upper limit of normal. Patients with CNS metastases other than leptomeningeal disease were eligible only if they were asymptomatic without corticosteroids. Prior radiotherapy outside of indicator lesions was allowed but has to be ended at least 4 weeks before starting chemotherapy. Concurrent radiation for palliation of bone or brain lesions was not allowed unless discussed with the medical monitor. Other inclusion criteria included absence of uncontrolled cardiovascular, infectious, psychiatric, neurologic or metabolic illnesses, lack of history of hypersensitivity reaction to polysorbate 80, and of other malignances with the exception of adequately managed cutaneous basal cell carcinoma or in situ uterine cervix carcinoma.

2.2. Study design

The trail was designed as a randomized phase II multicenter trial, which randomly assigned eligible patients in a 1:1 ratio to receive cisplatinum-based chemotherapy doublets including VNR or DCT. Sample size was evaluated according to Fleming's single-stage formula [20]. For a power of 90% against the hypothesis of a positive QoL response rate >40% and a 5% false positive rate against a response rate of <20%, 42 patients per arm had to be enrolled in the study. The institutional review board at each site approved the protocol. Each patient provided written informed consent. Primary endpoints were analysis of quality of life and symptoms control rate, and evaluation of chemotherapy-related side-effects. Secondary endpoints included objective responses, time-to-progression, time-to-treatment failure, overall survival.

2.3. Treatment plan

Patients enrolled in arm A received CDDP 75 mg/m^2 with an adequate pre- and post-hydration protocol with forced diuresis on day 1 plus DCT 75 mg/m^2 on day 1 every 3 weeks as previously described [13]. Patients enrolled in arm B received CDDP 80 mg/m^2 with an adequate pre- and post-hydration protocol with forced diuresis on day 1 plus VNR 30 mg/m^2 on days 1 and 8 as i.v. bolus every three weeks as previously published [15]. All patients received an identical anti-emetic treatment with ondansetron plus dexamethasone. Granulocyte-colony stimulating factor (G-CSF) and/or erythropoietin (EPO) were employed as needed depending on single cases need and investigator decision, but their use had to be reported in details and communicated to the study monitor. Patients were restaged for objective response after the first 3 cycles of chemotherapy. Patients with complete or partial response or stabilization continued treatment until disease progression or a maximum of 6 cycles in the absence of unacceptable toxicity. Patients progressing before or at first evaluation were shifted to a second-line treatment depending on single researcher's decision. Unacceptable toxicity was defined as the occurrence within the first three cycles of any of the following: grade 4 anemia or vomiting or mucositis or diarrhea, or constipation or fatigue or fever, any other grade 3–4 toxicity excluding hair loss, any toxicity inducing a severe worsening of general condition that prevented restaging, any toxicity that in the judgment of physicians induced early suspension of treatment for reasons other than progression.

2.4. Assessments

Health-related QoL was assessed at entry and after every cycle using the EORTC QLQ-C30 self-report instrument that includes a