Second-line chemotherapy for non-small cell lung cancer

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Despite being considered a standard of care, administration of second-line chemotherapy for non-small cell lung cancer is limited to patients in good performance status (ECOG PS 0–1) and to selected patients with PS 2. Drugs currently approved by FDA in this setting are docetaxel, gefitinib, erlotinib and pemetrexed, while in Europe those registered with this indication are only docetaxel and pemetrexed. This short review will focus on the role of pemetrexed, from the controlled phase II trial, to the development of the vitamin supplementation strategy to decrease toxicity, to the large phase III registration trial undertaken vs. the standard docetaxel. Moreover, the huge patient material collected during this latter trial has lead to further analyses to clarify several aspects of second-line treatment, from toxicity to quality of life assessment, to its role in elderly patients and to the direct translation in terms of costs. Finally, we will give a brief overview on current trials, that mainly explore the possibility to raise pemetrexed dose, and thus to increase its activity while maintaining an acceptable toxicity.

Key words: second-line chemotherapy, NSCLC, pemetrexed, docetaxel

Introduction

Second-line chemotherapy for non-small cell lung cancer (NSCLC) can be considered a standard of treatment in patients progressing after a front-line therapy, but still maintaining a good performance status (PS). Two phase III trials undertaken in the 90s have demonstrated how docetaxel, administered i.v. at 75 mg/m² in a 3-week schedule, can improve survival and quality of life compared to best supportive care alone [1] or to an alternative single-agent treatment, i.e. vinorelbine or ifosfamide [2]. In both these studies, docetaxel reached a response rate of approximately 6%, with a median survival and a 1-year survival rate of almost 7 months and 30% respectively. Despite a significant improvement in quality of life scores concerning pain control, weight loss and PS, obtained with docetaxel vs. the control group, toxicity of docetaxel was not irrelevant. Grade 3–4 neutropenia and febrile neutropenia were the dose limiting toxicities occurring in 54–67% and in 1.8–8% of patients respectively. In order to increase docetaxel tolerability, while maintaining a comparable activity, several trials have explored different schedules of docetaxel administered weekly. Though the first end-point has been fulfilled, survival data from randomized phase II and phase III trials are still contradictory [3–6]. A need for new drugs, active in this setting was thus becoming mandatory.

Pemetrexed is a multi-targeted antifolate that strongly inhibits three enzymes involved in the synthesis of purines and pyrimidines: thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT). Apart from its specific activity, the high affinity of pemetrexed for the reduced folate carrier guarantees an efficient transport of the drug into cells, and its low affinity for exporters (i.e. multidrug resistance-associated proteins) helps to maintain a high level of active compound within the cell [7].

Though pemetrexed has shown to be active in a variety of tumour types, in this short review we will focus only on its role as single-agent chemotherapy for NSCLC, in the setting of second-line treatment.

Clinical trials with single-agent pemetrexed

In a large phase II trial [8], pemetrexed was administered at 500 mg/m² every 3 weeks to a very selected cohort of NSCLC patients, with a particularly aggressive disease, i.e. progressing during or within 3 months after completion of first-line treatment, but with still a good ECOG PS (0–1). Among the 79 evaluable patients, 8.9% responded to pemetrexed, with a higher response rate in patients who had not received platinum as first-line treatment (14.5%) compared to patients who had (4.5%). Median survival time and 1-year survival rate in the overall group were 5.7 months and 23% respectively. As in previous trials, even in this study the dose-limiting toxicities were myelo-suppression and skin rush. The systematic pre- and postmedication of pemetrexed with oral corticosteroids reduced the incidence of grade 3 skin rush to
only 4 patients, but grade 3–4 neutropenia was experienced by 35% of patients. Moreover, 3 patients died of septic complications following severe neutropenia.

Subsequently, with the aim of identifying the molecular basis of toxicity during antifolate treatment, Niyikiza et al. [9] found that pre-treatment plasma levels of homocysteine were directly associated with severe myelotoxicity. Moreover, homocystein was an indirect measure of folate and vitamin B12 status of patients. Thus, in a prospective cohort, with a supplementation of oral folic acid and intramuscular B12 a sensitive reduction of homocysteine plasma levels as well as of hematological toxicity of pemetrexed was observed.

With these premises, a phase III registration trial was undertaken to demonstrate the non-inferiority of pemetrexed as second-line treatment when compared to the standard triweekly docetaxel [10]. In a 1-year period, starting March 2001, 571 patients resistant to front-line chemotherapy were randomized in the study. The primary objective was overall survival, but secondary objectives included not only response rate, time-to-progression and toxicity, but also quality of life scores and use of concomitant supportive measures.

Pemetrexed, administered with the same schedule as the phase II trial plus vitamin supplementation, showed to be non-inferior to docetaxel in terms of efficacy. Median overall survival, response rate and 1-year survival rate were in both arms approximately 9 months, 9% and 30% respectively. The best prognostic factors were PS (0–1 vs. 2), stage of disease (IIIB vs. IV) and time since last chemotherapy (<3 months vs. ≥3 months). Moreover, a further retrospective analysis on pooled data from both arms assessed a prognostic impact of previous chemotherapy on the outcome of second-line treatment. In this analysis, patients treated with first-line platinum/gemcitabine had a longer overall survival from second-line randomization than patients treated with other doublets (9.1 vs. 7.6 months, respectively) [11].

Though only as secondary end-points, the most interesting data came from the analysis of toxicity results. Safety profile of pemetrexed was significantly better than that of docetaxel. Patients treated with docetaxel were more likely to experience grade 3–4 neutropenia (40.2% vs. 5.3%), febrile neutropenia (12.7% vs. 1.9%) and infections associated with neutropenia (3.3% vs. 0%) than patients treated with pemetrexed. In this latter group, fewer patients required hospitalization due to neutropenic fever (1.5% vs. 13.4%) and thus there was a more limited use of white blood cells growth factors (2.6% vs. 19.6%) compared to patients who received docetaxel.

Nevertheless, reporting toxicity results as a percentage of patients experiencing a certain adverse event gives important information at a population level, but might not reflect the real impact of drug-related toxicity on single patients, in terms of severity and duration. Thus, in a recent report, toxicity data from this very phase III trial have been analyzed in terms of mean time patients could expect to spend with or without adverse events while receiving chemotherapy [12]. Compared to patients who received docetaxel, patients treated with pemetrexed had a shorter mean time with drug-related toxicity: 2.1 days vs. 10 days and 0.9 days vs. 14.9 days for grade 3 and 4 hematological toxicity respectively, and 4.6 days vs. 10.3 days and 0.3 days vs. 1.2 days for grade 3 and 4 non-hematological toxicity respectively.

Another important sub-analysis of this trial concerns elderly patients [13]. As observed in first-line studies, even in this trial the representation of elderly patients was 15%, significantly lower than that in the general lung cancer population, where median age is 65 years. Nevertheless, though highly-selected, interesting results rise from this subset of patients. There were no significant differences in outcome between elderly and younger patients. Response rate was slightly lower in the elderly population (3% vs. 9%) but survival was equivalent among the two groups. Same considerations can be done for toxicity. In the pemetrexed arm, elderly patients had a higher incidence of grade 3–4 neutropenia compared to younger patients (12.5% vs. 4%), though it was still lower than that experienced by elderly patients in the docetaxel arm (29.7%). Of concern in this latter group was the incidence of febrile neutropenia, which was registered in 18.9% of cases, higher compared to that of younger patients treated with docetaxel (11.7%) and to that of elderly patients treated with pemetrexed (2.5%).

The third main secondary end-point in the study by Hanna et al. was the evaluation of quality of life scores, assessed with the Lung Cancer Symptoms Scale (LCSS) questionnaire. Both arms reached the same scores in terms of symptom palliation. Moreover, a further analysis showed that the average symptom burden index (ASBI), defined as the average of the 6 symptom-specific questions from the LCSS concerning fatigue, anorexia, pain, cough, dyspnea and hemoptisis was directly related with tumor response to second-line chemotherapy. Without differences between study arms, patients who showed a CR or PR had an improvement in the ASBI from baseline of 9.9 points, significantly higher than the improvement achieved by patients with SD (4.3 points), while patients with PD worsened (−3.7 points) [14].

Finally, when treatment has mainly a palliative end-point, the translation that it has in terms of costs is remarkable, not only due to the drug itself, but also to the supportive care necessary to face drug-related toxicities. To explore this issue, resource utilization data (hospital admissions, concomitant medications, transfusions) were collected from patients who in Hanna et al. trial were actually treated for at least one cycle (541 patients). To simplify the analysis and to reduce obvious differences between the countries involved worldwide in the trial (from Pakistan to US), costs were calculated using the perspective of the national health care system in Italy. It was then shown that the already mentioned lower toxicity experienced by patients treated with pemetrexed translated directly into cost savings. The estimated mean cost of toxicity management per patient was 367 Euros in pemetrexed arm, and 1385 Euros in docetaxel arm. This striking difference was mainly due to the increase in hospitalization and concomitant medications performed in an outpatient setting during docetaxel treatment [15].

**ongoing studies on pemetrexed**

Current ongoing studies with pemetrexed are exploring the possibility to increase the dose while still maintaining an
acceptable toxicity profile. This is based on the following simple considerations. Pemetrexed dose in the already described phase III trial was chosen after proper phase I studies had assessed pemetrexed maximum tolerated dose. Nevertheless, these trials were undertaken without any vitamin supplementation. Afterwards, the favorable toxicity profile registered in Hanna et al. study, with pemetrexed at 500 mg/m² plus constant vitamin and folic acid supplementation, has provided the background for further dose-escalation studies.

Presently, several phase I trials are exploring higher doses of pemetrexed with different schedules of vitamin supplementation. Besides, a phase III multicenter controlled randomized trial is addressing the question of possible gaining in activity. Patients are randomized in a 1:1 fashion to receive pemetrexed at 500 mg/m² q3w (control group) or at 900 mg/m² q3w (study group), and the main end-point is overall survival. The trial is currently accruing.

conclusions

Drugs presently approved by FDA for the treatment of NSCLC after the first-line setting are docetaxel, gefitinib, erlotinib and pemetrexed. In Europe, the registration for this setting is limited to docetaxel and pemetrexed. Gefitinib, at the dose of 250 mg/d p/os, had a fast-track registration following the positive results of two phase II randomized trials [16, 17]. In these studies, response rate ranged from 12% to 20%, and median survival time from 7 to 8 months. Unfortunately, similar good results have not been confirmed by a recently reported phase III multicenter randomized trial where gefitinib was challenged vs. placebo (ISEL Study) [18]. Due to these negative results, in order to consider the registration of erlotinib for this setting. Exploring the reasons of this discrepancy between the two inhibitors of the epidermal growth factor receptor is beyond the scopes of this paper. Nevertheless, as shown in Figure 1, pemetrexed is the only compound that has been approved after a direct challenge with an active drug in this setting, i.e. docetaxel, used as control group in the contest of a phase III randomized trial, and not vs. best supportive care alone.

For this reason pemetrexed can be considered a standard of care for second-line chemotherapy in advanced NSCLC in Europe.

disclosures

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references