educational session

The expanding role of systemic treatment in NSCLC

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2nd line treatment and beyond

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Annals of Oncology 17 (Supplement 10): x97–x100, 2006
doi:10.1093/annonc/mdl245

Non-small cell lung cancer: second-line and beyond

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introduction

Based on randomized trials and meta-analyses the – albeit limited – benefit of first-line chemotherapy for fit patients with advanced and metastatic non-small cell lung cancer has been firmly established. The concomitant or sequential chemotherapy and radiotherapy for patients with locally advanced but inoperable tumors (Stage IIIB) has become the recommended treatment for patients with a good performance status and there is compelling evidence that patients with operated stage IB to IIIA disease may benefit from adjuvant chemotherapy. As a consequence, today most patients with non-small cell lung cancer will receive some form of chemotherapy at the time of diagnosis and – since all patients with advanced disease and a proportion of patients with localized disease at presentation will experience tumor relapse, many of them in good general condition – the question of second-line chemotherapy will be encountered with increasing frequency.

Considering the literature of patients treated with second-line chemotherapy, one has to be aware of the heterogeneity of the patient population. While the selection criteria of most trials require a performance status of 0 to 2 and patients with co-morbidity are excluded, the patients may still be quite heterogeneous since the indication of first-line chemotherapy may range from combined modality therapy for locally advanced disease to metastatic disease. Second-line chemotherapy for patients who received adjuvant chemotherapy will certainly become an issue in the near future.

For patients initially treated for advanced disease, a distinction has to be made between patients with primary refractory tumors and patients with relapse after response to first-line treatment. While in other tumors types such as in malignant lymphoma, there is a consensus how these groups of patients are defined no such consensus has yet been established for non-small cell lung cancer. The recommended first-line chemotherapy for fit patients with non-small cell lung cancer is a platinum-based two-drug combination. However, this continues to be a matter of debate and some patients are treated upfront with non-platinum combinations which increases the heterogeneity of patients considered for second-line treatment.

Given the recent results of epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, patients with non-small cell lung cancer cannot be considered as one group in relation to systemic therapy. Increasingly, clinical and molecular characteristics will also be used to identify patients who might benefit from a certain form of treatment.

second-line chemotherapy for patients with advanced non-small cell lung cancer

survival advantage of docetaxel versus best supportive care

The database demonstrating a survival advantage of second-line chemotherapy compared to best supportive care is small. It originates from one landmark study at the National Cancer Institute of Canada comparing the use of docetaxel given every three weeks to best supportive care alone in patients with stage IIIB and IV non-small cell lung cancer after cisplatin-based first-line chemotherapy [1]. Requirements were a performance status of 0 to 2 and no symptomatic or uncontrolled brain metastasis. The trial included patients with response, no change and progressive disease during cisplatinum treatment. The dose of docetaxel was reduced from 100 mg/m^2 to 75 mg/m^2 after the identification of a high toxic death rate in the chemotherapy arm during interim safety monitoring. The median survival of the chemotherapy group was 7.0 months versus 4.6 months in the control group (log rank $P = 0.047$). The response rate for patients with measurable disease was 7.1%. There were no toxic deaths with the dose of 75 mg/m^2 and only one of 55 patients developed febrile neutropenia. Quality-of-life (QoL) was evaluated in this trial using the Lung Cancer Symptom Scale and the European Organisation for Research and Treatment (EORTC) quality-of-life questionnaire (QLQ–C30). Significant differences between the two arms favoring docetaxel were detected for pain scores and in the deterioration of the global QoL today score [2].

The cost-effectiveness of second-line docetaxel chemotherapy at 75 mg/m^2 has been estimated in two studies. Based on the perspective of the Canada's public health system the cost was $31 776 per life-year gained [3]. Viewed from the perspective of the United Kingdom National Health System (NHS) the cost per life-year gained was estimated to be £13 863 [4].

randomized studies comparing three-weekly docetaxel with other agents in second-line chemotherapy. Pemetrexed is an alternative

There are currently two phase III trials published comparing docetaxel chemotherapy at 75 mg/m^2 with other agents in second-line treatment. A phase III trial compared docetaxel at 100 mg/m^2 and 75 mg/m^2 with a control arm of either weekly vinorelbine or 3-weekly ifosfamide [5]. Response was 10.8% and

6.7% in the docetaxel arms and 0.8% in the control arm. Median survival in all treatment arms ranged between 5.5 and 5.7 months and there was no significant advantage in median survival for docetaxel at either dose and the major endpoint of superiority of docetaxel was not reached. However, the one-year survival was 21% with docetaxel 100 mg/m^2, 39% with docetaxel 75 mg/m^2 and 19% only in the control group ($P = 0.025$). Examining response rates by the stratification factors prior docetaxel, best response to platinum and performance status did identify significant correlations.

A phase II study of the multi-targeted antifolate pemetrexed in patients who progressed during or within 3 months after first-line chemotherapy showed a response rate of 8.9% and a median survival of 5.7 months [6]. This prompted a comparative phase III study of three weekly pemetrexed at 500 mg/m^2 versus docetaxel 75 mg/m^2 based on a non-inferiority design [7]. While there was no difference in response rates of 9.1% and 8.8% and median survival times of 8.3 months and 7.9 months, respectively, there was a difference in the toxicity profile with lower rates of neutropenic fever, neutropenic infections, hospitalization due to drug-related side effects, use of granulocyte colony stimulating factor and alopecia in favor of pemetrexed. Thus docetaxel and pemetrexed have comparable efficacy in second-line therapy of non-small cell lung cancer with a toxicity profile favoring pemetrexed.

is there an advantage for weekly docetaxel?

One randomized phase II trial and two randomized phase III trials compared weekly docetaxel 40 mg/m^2 with the standard 3-weekly schedule of docetaxel at 75 mg/m^2. The randomized phase II trial showed similar response rates of 3.2% versus 4.8% and median survival times of 5.5 months versus 5.8 months in the weekly as compared to the 3-weekly arm. Febrile neutropenia was not encountered in the weekly arm, while it was documented in 6.5% of patients in the 3-weekly arm [8]. The major endpoint of the first phase III study comparing weekly docetaxel at 33 mg/m^2 with the standard 3-weekly arm was QoL at 3 weeks [9]. No differences were observed in global QoL scores. However there was a statistical significant difference favoring weekly docetaxel in regard to hair loss, pain and cough, and a significant difference favoring 3-weekly docetaxel in relation to diarrhea. Survival was the major endpoint of the second phase III study comparing weekly docetaxel at 35 mg/m^2 with the 3-weekly arm [10]. Response rates were similar with 10.5% versus 12.6% while the median survival times of 9.2 months versus 6.3 months showed a trend favoring the weekly docetaxel arm. There was significantly less hematological toxicity in the weekly arm. Based on these studies, docetaxel given weekly has similar efficacy as the conventional 3-weekly schedule but slightly better control of pain and cough and potentially slightly less hematological toxicity. In the selection between these regimens, ease of access to ambulatory care and patient preference remain decision factors.

activity of other single agents

An extensive review on second-line chemotherapy for advanced non-small cell lung cancer has recently been published which outlines the results of the many phase II trials [11]. Paclitaxel weekly at 80 mg/m^2 has been examined side to side with docetaxel weekly at 36 mg/m^2 in a small randomized phase II study in patients with prior cisplatin therapy [12]. Median survival was 3.2 months with paclitaxel and 6 months with docetaxel. However, the study was too small to allow definite conclusions. The lack of efficacy of paclitaxel in the second-line setting was also reported from a large phase II study with a response rate of 3% and a median survival of 4.5 months [13].

Two of the three reports with vinorelbine, given weekly as second-line treatment, reported no responses, suggesting that this drug does not have major activity in this setting. This is supported by the study of Fossella, in which the response rate in the control arm of vinorelbline or ifosfamide was 0.8% only [5].

Gemcitabine has been examined in second-line treatment in three phase II studies [14–16]. Response rates ranged between 6 and 20% and median survival times between 3.9 and 7.8 months, suggesting that this agent might be active in this setting.

combination or single agent in second-line treatment?

Only randomized studies will be able to answer the question whether combination chemotherapy would result in a better outcome than single agent therapy. Studies available so far all document increased toxicity for the combination without improvement of survival or QoL.

Two studies compared the results of 3-weekly docetaxel with or without the addition of irinotecan and found significantly increased gastrointestinal toxicity with the combination [17, 18].

Another study examined cisplatin with or without irinotecan in patients pretreated with gemcitabine and docetaxel [19]. While the response rate was 22.5% for the combination versus 7% for cisplatin alone, there was no difference in survival and QoL measurements, but significantly more febrile neutropenia with the combination.

The toxicity of a combination of weekly docetaxel and vinorelbine has been shown in another study comparing this combination with weekly docetaxel and gemcitabine in second-line treatment [20]. The vinorelbine arm had to be terminated early because of neutropenic fever in 70% of the patients. The combination of docetaxel and gemcitabine was better tolerated. However, neither response nor survival was better than with single agent treatment. For the time being, combination chemotherapy in second-line treatment remains experimental and is not recommended outside clinical trials.

characteristics of patients treated with second-line therapy

Based on the selection criteria in clinical studies, patients in studies with second-line therapy of non-small cell lung cancer are certainly not representative of all patients, for whom the question of further therapy arises. A recent study examined which of the patients with stage IIIB or IV non-small cell lung cancer who participated in a phase III trial of paclitaxel and carboplatin were likely to receive second-line treatment [21]. Forty-four percent of patients were treated with second-line chemotherapy and multivariate analysis showed higher baseline performance status, female sex, non-squamous cell histology and having received two or more cycles of chemotherapy to be

associated with second-line chemotherapy, while early termination of first-line chemotherapy decreased the likelihood of further therapy. Another retrospective analysis examined the outcome in 43 patients who had received more than two prior chemotherapy regimens [22]. Response rates were reported for 21% of these patients in first-line, for 16% in second-line, 2% in third-line and 0% in fourth-line. The median survival from the start of the last – either third or fourth – treatment was 4 months.

new therapeutic approaches targeting the epidermal growth factor receptor

The effect of orally administered EGFR tyrosine kinase inhibitors has shifted the attention of patients and physicians to the potential of molecular therapies for second-line treatment of non-small cell lung cancer. The reports of two large phase II trials on the activity of gefitinib at two dose levels in patients with cisplatin-pretreated non-small cell lung cancer raised the hope for the possibility of a new therapeutic approach beyond conventional chemotherapy [23, 24]. An unexpected response rate of 10 to 20% was documented in patients heavily pretreated with chemotherapy, and symptom improvement was seen in 43% of patients at a daily dose of 250 mg. Side effects were mild and included skin rash and diarrhea. Because of similar response rates at 500 mg and 250 mg, but increased toxicity at the higher dose level, a dose of 250 mg was chosen for further studies. Clinical parameters associated with response were female sex, never smokers, adenocarcinoma, and Japanese origin.

A similar phase II study with erlotinib at a daily dose of 150 mg also demonstrated a response rate of 12% and a possible association of survival and the development of skin rash was reported [25].

Both agents were subsequently examined in placebo-controlled randomized phase III studies in patients with non-small cell lung cancer pretreated with one or two chemotherapy regimens with the aim to detect a 33% improvement in survival [26, 27]. This was reached in the erlotinib study with median survival times of 6.7 months versus 4.7 months (hazard ratio 0.7, 95% confidence interval (CI) 0.58–0.85), but just missed in the gefitinib study with median survival times of 5.6 months versus 5.1 months (hazard ratio 0.89, 95% CI 0.77–1.02). Response rates were 8.9% in the erlotinib and 8% in the gefitinib study. In the erlotinib study multiple regression analysis identified a history of never smoking and the presence of adenocarcinoma (as well as EGFR expression with data available only in 43% of patients) with response. Longer survival was associated with erlotinib treatment, Asian ethnicity, adenocarcinoma and a history of never smoking. In the gefitinib study a pre-planned subgroup analysis demonstrated a survival advantage for gefitinib in never smokers and patients of Asian origin.

The discovery of mutations in the EGFR in patients with a dramatic tumor response to gefitinib not only pointed to a new molecular entity of non-small lung cancer, but has also raised the hope of identifying patients with a high likelihood of response and benefit from a systemic treatment based on a laboratory analysis [28, 29]. Mutations of the EGFR involve deletion mutations in exon 19 in about half of the patients, missense mutations in exon 21 in about 40% and mutations in exon 10 and 20 in about 10% of patients [30, 31]. The rate of patients with mutations is about 10% in Europe and North America and 30% in Asian countries. Mutations are associated with adenocarcinoma, female sex, and a history of non-smoking. Response to gefitinib or erlotinib is associated with the presence of these mutations.

More recently, amplification of the EGFR gene has also been associated with response to gefitinib [32]. Molecular examinations of tumors from patients participating in the erlotinib versus placebo trial confirmed the association of EGFR mutations with response and identified the association of EGFR amplication with survival [33].

Which of the molecular test or combination of tests ultimately will best serve to identify patients with tumor sensitive to therapy cannot be conclusively stated yet.

Given the results of these phase III studies and numerous phase II studies it is irrefutable that EGFR tyrosine kinase inhibitors are active and provide symptom improvement in patients with chemotherapy pretreated non-small cell lung cancer. The major question, which needs to be addressed now, is to whom such a treatment should be offered. While there are advocates for the general use of these agents in second-line lung cancer, many feel that patients should be selected based on clinical features or molecular characteristics. Whether the treatment outcome for patients selected on the basis of a molecular study would be superior to the selection based on clinical characteristics remains to be determined.

Advances in this field over the past 3 years have been rapid, and other agents, including other tyrosine kinase inhibitors and monoclonal antibodies are being investigated in second-line treatment of patients with non-small cell lung cancer. With better knowledge about the interaction between inhibitors and mutated receptor, agents might be identified which provide a response in patients developing resistance to gefitinib or erlotinib [34]. Although EGFR antibodies are being examined as single agent or in combination for second-line treatment of non-small cell lung cancer, definitive results have not yet been published [35].

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