Chemotherapy of advanced non-small cell lung cancer in elderly patients

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Non-small cell lung cancer (NSCLC) may be considered typical of advanced age. More than 50% of NSCLC patients are diagnosed over the age of 65 and approximately one-third of all patients are over the age of 70. Elderly patients tolerate chemotherapy poorly compared to their younger counterpart because of the progressive reduction of organ function and comorbidities related to age. For this reason, these patients are often not considered eligible for aggressive platinum-based chemotherapy, the standard medical treatment for advanced NSCLC. With the current evidence, in clinical practice, single-agent chemotherapy with a third-generation drug (vinorelbine, gemcitabine, taxanes) should be the recommended option for non-selected elderly patients with advanced NSCLC. Subset analyses suggest that the efficacy of platinum-based combination chemotherapy is similar in fit older and younger patients, with an acceptable increase in toxicity for elderly patients. However, feasibility of platinum-based chemotherapy remains an open issue and has to be proven in prospective randomised trials. High priority should be also given to the evaluation of the role of new targeted therapies. Moreover, a comprehensive geriatric assessment for individualized treatment choice in NSCLC elderly patients is mandatory.

Key words: NSCLC, elderly patients, chemotherapy, lung cancer

introduction

Lung cancer is the most common cancer in the world and the leading cause of cancer-related deaths in Europe and in other Western countries [1]. Lung cancer may be considered typical of advanced age. More than 30% of lung cancer patients are diagnosed over the age of 65 and about 30% over the age of 70 [2, 3].

Since most patients with non-small cell lung cancer (NSCLC) have advanced disease at diagnosis, chemotherapy is the mainstay of management. In current practice, the elderly, usually excluded from participation in clinical trials, receive untested or inadequate treatment, based on a long-held but completely undocumented notion that cancers in older people are less aggressive [4].

Elderly patients often present with medical and physiological characteristics that make the selection of their optimal treatment more challenging. Unfortunately, because of this, these patients are at risk of being under-treated [5].

The evidence regarding the tolerability and efficacy of anticancer treatments for elderly patients affected by NSCLC comes from two different types of publications: prospective clinical trials specifically designed for the elderly and, retrospective analyses conducted on the subgroup of elderly patients enrolled onto clinical trials that did not have an upper age limit. For the latter type of studies, it is easy to argue that when a clinical trial is designed to test the efficacy of a treatment intended for younger patients, only a selected proportion of elderly patients will be considered for enrolment, and so the results may not necessarily extend to the general non-selected elderly population [6].

single agent chemotherapy

The introduction into clinical practice of new, active and well-tolerated drugs has stimulated clinical research. The first randomized phase III trial in advanced NSCLC elderly patients was the Elderly Lung cancer Vinorelbine Italian Study (ELVIS). In this trial, 161 chemotherapy-naı¨ve patients (≥70) were randomized to receive vinorelbine (30 mg/m² on days 1 and 8, every 3 weeks) or best supportive care [7]. A significant survival advantage with a better quality of life (QoL) was observed for vinorelbine compared with the control group (median survival time [MST]: 27 versus 21 weeks, P = 0.04). Patients treated in the vinorelbine arm scored better than controls on many QoL subscales. Therefore, in elderly patients with advanced NSCLC palliative chemotherapy should be considered.

Also gemcitabine and taxanes (paclitaxel and docetaxel) have demonstrated activity and tolerability in the treatment of advanced NSCLC [8].

Recently, in a randomized phase III trial vinorelbine 25 mg/m² days 1 and 8 every 3 weeks was compared to docetaxel 60 mg/m² day 1 every 3 weeks in the treatment of advanced NSCLC.
elderly patients. A total of 181 patients were randomized. Docetaxel provided better objective response rate (ORR) (22.7% versus 9.9%, respectively; \( P = 0.019 \)), and MST than vinorelbine (13.9 months versus 9.9 months, respectively; \( P = 0.038 \)) with improvement of disease related symptoms. Major toxicity was grade 3–4 neutropenia in both arms, 83.0% in docetaxel, and 69.2% in vinorelbine group (\( P = 0.031 \)). This is the first trial in which a single-agent treatment results superior to another one but, further larger phase III trials needed to confirm these results [9].

**non–platinum-based polichemotherapy**

In order to improve the results obtained with single-agent chemotherapy, some non-platinum-based combinations have been developed. The most studied non-platinum-based regimen is gemcitabine plus vinorelbine. Two phase III trials have compared gemcitabine plus vinorelbine combination with a single-agent therapy [10, 11]. A small study of gemcitabine 1200 mg/m\(^2\) alone (\( n = 120 \) patients) closed early when an interim analysis showed that the combination conferred a significant survival advantage over the single agent (MST: 29 versus 18 weeks, \( P < 0.01 \)) and a better ORR [10]. However, the 18-week survival for single-agent vinorelbine in this study is markedly lower than the 28- to 38-week survival times reported in six large randomised trials, including three studies dedicated entirely to elderly patients [8, 9]. The Multicenter Italian Lung cancer in the Elderly Study (MILES) trial, enrolling 700 patients with NSCLC, is the largest phase III study of the elderly published to date [11]. Patients were randomised to receive single-agent chemotherapy with vinorelbine 30 mg/m\(^2\) or gemcitabine 1200 mg/m\(^2\) or combination therapy with vinorelbine 25 mg/m\(^2\) plus gemcitabine 1000 mg/m\(^2\), all treatments recycled every 3 weeks. Combination treatment had no advantage in terms of ORR, time to progression (TTP), MST or QoL over single-agent therapy. Moreover, although toxicity was considered acceptable in all groups, it was higher with the combination than with the single agents. The authors concluded that single-agent therapy with vinorelbine or gemcitabine is preferable to the combination for treatment of advanced NSCLC in elderly patients.

Table 1 summarises the randomized phase III trials performed in advanced NSCLC elderly patients.

### platinum-based chemotherapy

Cisplatin administration is associated with significant toxicity and the evaluation of the risk versus benefit ratio should be particularly rigorous in elderly patients. The benefit of platinum-based combination chemotherapy should be proven by clinical trials specifically designed for elderly patients. These studies are still lacking, and evidence to support the use of platinum agents in elderly patients with advanced NSCLC comes only from several retrospective analyses of the subgroup of elderly patients enrolled onto randomized trials without an upper age limit in the inclusion criteria. Overall, these analyses show a similar outcome of platinum-based therapy for elderly patients compared with their younger counterparts, in terms of ORR and MST, with similar toxicity and no significant adverse effect on QoL [12]. It is important to note, however, that the percentage of elderly patients enrolled onto these studies with cisplatin did not exceed 20% of the actual study population.

Interesting prospective results were obtained in elderly patients with the combination of cisplatin plus a third-generation chemotherapy drugs (gemcitabine, vinorelbine, docetaxel) [12].

Several recently published phase II studies of combination chemotherapy based on modified schedules of carboplatin (low-dose or weekly administration) have shown a reasonable level of activity and tolerability, too [12].

We evaluated the role of cisplatin-based chemotherapy in advanced NSCLC elderly patients in the MILES 02 phase II randomised trial, in which the patients could receive single-agent gemcitabine 1200 mg/m\(^2\) at fixed-rate infusion (10 mg/m\(^2\)/min) or cisplatin (administered at attenuated doses of 50, 60 or 70 mg/m\(^2\)) plus either gemcitabine 1000 mg/m\(^2\) or vinorelbine 25 mg/m\(^2\). The trial reached the planned accrual of 210 patients and after having analysed the results of this phase II study, a phase III trial should be developed [13].

<table>
<thead>
<tr>
<th>Author</th>
<th>Regimen</th>
<th>Age (years)</th>
<th>No.pts</th>
<th>RR (%)</th>
<th>MST (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELVIS trial, 1999</td>
<td>Vinorelbine vs. Best Supportive Care</td>
<td>≥70</td>
<td>76</td>
<td>20</td>
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<tr>
<td>Frasci, 2000</td>
<td>Vinorelbine vs. Best Supportive Care</td>
<td>≥70</td>
<td>78</td>
<td>NA</td>
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</tr>
<tr>
<td>Gridelli, 2003</td>
<td>Vinorelbine + Gemcitabine vs. Vinorelbine</td>
<td>≥70</td>
<td>60</td>
<td>15</td>
<td>4.2</td>
</tr>
<tr>
<td></td>
<td>+ Gemcitabine vs. Vinorelbine + Gemcitabine</td>
<td></td>
<td>60</td>
<td>22</td>
<td>6.7</td>
</tr>
<tr>
<td>Takeda, 2005</td>
<td>Vinorelbine vs. Docetaxel</td>
<td>≥70</td>
<td>232</td>
<td>21</td>
<td>6.9</td>
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<td></td>
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<td>8.365</td>
</tr>
</tbody>
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ELVIS, Elderly Lung cancer Vinorelbine Italian Study; RR, response rate; MST, median survival time; NA, not applicable.

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**Table 1. Results from phase III trials of advanced non-small-cell lung cancer in elderly patients**

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targeted therapies

Gefitinib (ZD1839, Iressa) and erlotinib (OSI774, Tarceva), two orally available selective and reversible inhibitors of epidermal growth factor receptor (EGFR) tyrosine kinase, have demonstrated activity as single-agent therapy in heavily pretreated patients with NSCLC [8]. The combination of gefitinib with either vinorelbine or gemcitabine was investigated in a prospective study of 60 patients aged ≥70 years with advanced NSCLC. Gefitinib combined with gemcitabine showed low activity, but was generally well tolerated. In contrast, toxicity was unacceptable in the vinorelbine arm in which 18 of 25 patients (72%) had grade 4 neutropenia, and there were 3 treatment-related deaths with no ORR reported [14]. Very recently, erlotinib has been tested prospectively in a phase II study in patients aged more than 70 years with previously untreated advanced NSCLC. Preliminary results on 30 patients, suggest that erlotinib is well tolerated with encouraging activity (ORR of 13.3%) as first-line treatment of advanced NSCLC of elderly patients. Adverse events were generally mild, although all responding patients developed a rash (which in 2 cases was severe) [15].

Our group is launching a randomized phase II study, named CALC-1 (Cetuximab in Advanced Lung Cancer), in which cetuximab (IMC-C225), a human-mouse chimeric anti-EGFR monoclonal antibody, is administered in combination with gemcitabine or gemcitabine followed by cetuximab in advanced NSCLC patients unsuitable for combination chemotherapy [13].

conclusion

A new generation of clinical trials specifically designed for the elderly population are needed and should include the development and validation of new measures and tools to define ‘biological’ vs ‘chronological’ age. Moreover, several treatment options should be evaluated such as non-platinum-based combination chemotherapy; platinum-based combination chemotherapy; new biologic agents [12].

With the evidence currently available from large randomised trials, single-agent chemotherapy with a third-generation agent can be considered a recommended option for elderly advanced NSCLC patients [16, 17]. However, which single-agent? Several factors should be considered by the clinician when choosing the drug to be administered. This choice should take into account the expected toxicity profile of the agent, pharmacokinetics, organ function and co-morbidities.

Platinum-based chemotherapy may represent a valid option for fit elderly patients with adequate organ function. Obviously, a proper selection of these patients is mandatory and further experimental evidence on this topic appears essential. Randomized phase III trials with adequate power to address the main questions regarding the efficacy and tolerability of platinum-based chemotherapy in advanced NSCLC elderly patients are needed, especially in selected elderly good performance status patients [12]. Moreover, in order to better define elderly patients enrolled in clinical trials, every patient should receive a complete functional assessment at baseline allowing a clearer interpretation of trial results.

references