Treatment of advanced non-small-cell lung cancer patients with ECOG performance status 2: results of an European Experts Panel

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Background: Platinum-based combination chemotherapy is currently recommended as the standard treatment for patients with advanced non-small-cell lung cancer (NSCLC), but its benefit seems limited to fit patients with a performance status (PS) of 0 or 1. For PS2 patients, there is no consensus on standard treatment. With the aims of reviewing the evidence supporting each of these therapeutic options, possibly reaching a consensus for treatment of PS2 patients affected by advanced NSCLC in clinical practice, and suggesting the priorities for clinical research in this field, an European Experts Panel took place in Avellino, Italy in April 2003.

Results and conclusions: On the basis of current evidence, chemotherapy treatment appears justified for patients with advanced NSCLC and PS2. Single-agent chemotherapy (gemcitabine, vinorelbine, taxanes) could be the preferred option, although carboplatin-based or low-dose cisplatin-based doublets may represent alternative options. Stronger evidence is expected from new clinical research specifically focused on PS2 patients. Single-agent chemotherapy should be the standard arm against which experimental treatments are tested in randomised trials dedicated to PS2 patients. High priority should be given to the evaluation of tolerability and efficacy of platinum-based combinations, and to the testing of new biological agents. Another research priority is the improvement of supportive care. Patients strongly need symptomatic improvement: end points such as symptom relief, clinical benefit and quality of life should have a central position in trials dedicated to PS2 NSCLC patients.

Key words: advanced disease, chemotherapy, consensus, non-small-cell lung cancer, performance status 2

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 [1–3]. Non-small-cell lung cancer (NSCLC), including squamous carcinoma, adenocarcinoma and large-cell carcinoma, represents ~80% of all lung cancers. Unfortunately, at the time of diagnosis, the majority of patients already have metastatic disease and a systemic, palliative treatment is the only therapeutic option.

Performance status (PS) is a general, rough measure of the patient’s functional status. It measures the impact of tumour symptoms, together with other pre-existing medical problems and co-morbidities, on a patient’s daily function and ability of self-care. Several PS scales are available for clinical use: among them, those most commonly used are the Karnofsky’s scale [4], created at the beginning of chemotherapy era, and the Eastern Cooperative Oncology Group Scale of Performance Status (ECOG PS), a five-point scale (worsening from 0 to 5) based on the level of symptoms interference with normal activity and on the proportion of waking hours spent in bed [5] (Table 1). According to the latter scale, patients are classified as PS2 if they are restricted in physical activity, still ambulatory and capable of self-care but needing rest in bed, although for <50% of waking hours. PS2 patients usually account for a small proportion of patients enrolled in trials of first-line treatment for advanced disease [6–9] but represent a significantly higher proportion (up to 30–40%) when population-based surveys are conducted [10, 11].

In a meta-analysis evaluating the efficacy of chemotherapy in patients with NSCLC [12], cisplatin-based chemotherapy has shown a slight but statistically significant survival advantage over supportive care. According to the evidence that platinum-based combination chemotherapy can prolong survival, possibly improving quality of life (QoL) and controlling symptoms in these patients, it is currently recommended as the standard approach for patients with advanced NSCLC [13, 14]. However, the benefit achievable seems more evident for fit patients (PS0 or -1) and
The Materials and methods presented in this paper. Results and conclusions of that meeting are in this field, an European Experts Panel took place in Avellino clinical practice, and suggesting the priorities for clinical research susceptibility for treatment of PS2 patients affected by advanced NSCLC in chemotherapy. With the aims of reviewing the evidence support—combination chemotherapy; and platinum-based combination chemotherapy; single-agent chemotherapy; non-platinum-based patients are potential candidates: best supportive care without have to choose among several treatment options for which PS2 there is no treatment widely accepted as standard and oncologists based treatment for PS2 patients [13, 15]. For this latter sub-group, there is no consistent evidence about the real efficacy of platinum—based treatment for PS2 patients. Despite the recognised priority to include these end points in clinical trials regarding symptom relief and/or health-related quality-of-life benefits in PS2 patients, and retrospective information based on sub-group analysis from randomised clinical trials must be interpreted with caution [18], but currently there are no published prospective trials specifically dedicated to PS2 patients, and retrospective information based on sub-group analysis remains the best level of information on this topic available from the literature to date.

Another significant limitation of the published data is the lack of information regarding symptom relief and/or health-related quality-of-life benefits in PS2 patients. Despite the recognised priority to include these end points in studies for patients with advanced NSCLC our review showed that these data are hardly available.

The evidence available for each of the following six topics in the treatment of PS2 patients was reviewed: performance status as a prognostic factor; chemotherapy versus best supportive care; single-agent versus combination chemotherapy; non-platinum based versus platinum-based polichemotherapy; possible role of new biological agents; ongoing trials. Each topic was presented by one of the panellists and, after the discussion, a consensus was reached both for clinical practice suggestions and for clinical research priorities. Results and conclusions of the meeting were presented on 15 and 16 April 2003 to about 200 clinical oncologists coming from all over Italy.

Table 1. Most widely used performance status scales

<table>
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<tr>
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<tr>
<td>100</td>
<td>Normal with no complaints or evidence of disease</td>
</tr>
<tr>
<td>90</td>
<td>Able to carry on normal activity but with minor signs of illness present</td>
</tr>
<tr>
<td>80</td>
<td>Normal activity but requiring effort. Signs and symptoms of disease more prominent</td>
</tr>
<tr>
<td>70</td>
<td>Able to care for self, but unable to work or carry on other normal activities</td>
</tr>
<tr>
<td>60</td>
<td>Able to care for most needs, but requires occasional assistance</td>
</tr>
<tr>
<td>50</td>
<td>Considerable assistance and frequent medical care required; some self-care possible</td>
</tr>
<tr>
<td>40</td>
<td>Disabled; requiring special care and assistance</td>
</tr>
<tr>
<td>30</td>
<td>Severely disabled; hospitalization required but death not imminent</td>
</tr>
<tr>
<td>20</td>
<td>Extremely ill; supportive treatment and/or hospitalization required</td>
</tr>
<tr>
<td>10</td>
<td>Imminent death</td>
</tr>
<tr>
<td>0</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Relevant published papers reporting the results of randomised phase III clinical trials were obtained by Medline search. In order to obtain the largest amount of specific information on PS2 patients, some authors were contacted directly by the panel to obtain some data not available from the published papers. Abstracts from proceedings of the most important oncology meetings, not yet published as full papers, were also considered. Some of the data considered by the panellists still lack peer-review quality and are possibly not definitive.

The greatest part of the evidence analysed in the meeting comes from small sub-groups of patients with PS2, enrolled in clinical trials usually including patients with a PS ranging from 0 to 2. The proportion of patients with PS2 in these trials is often <20% of the whole study population, suggesting the existence of a selection bias determining the exclusion of PS2 patients with worse general conditions and co-morbidities. Median age of patients enrolled in randomised clinical trials is often significantly lower than that observed in clinical practice [16, 17], and eligibility criteria request good renal, hepatic and cardiac function, as well as absence of other significant co-morbidities. Consequently, it is not surprising that the proportion of PS2 patients in population-based studies—not biased by inclusion criteria and not restricted by the characteristics of experimental treatment—is consistently higher than that reported in the majority of clinical trials [10, 11]. The panellists are aware that sub-group analysis from randomised clinical trials must be interpreted with caution [18], but currently there are no published prospective trials specifically dedicated to PS2 patients, and retrospective information based on sub-group analysis remains the best level of information on this topic available from the literature to date.

The ‘European Experts Panel on the Treatment of Advanced NSCLC Patients with Performance Status 2’ was held at Avellino (Italy) on 14 April 2003. Eight oncologists from five European countries (France, Germany, Italy, The Netherlands and UK), with clinical and research experience in NSCLC, formed the scientific panel of the meeting.

Evidence available for each of the following six topics in the treatment of PS2 patients was reviewed: performance status as a prognostic factor; chemotherapy versus best supportive care; single-agent versus combination chemotherapy; non-platinum-based combination chemotherapy; and platinum-based combination chemotherapy. With the aims of reviewing the evidence supporting each of these therapeutic options, possibly reaching a consensus for treatment of PS2 patients affected by advanced NSCLC in clinical practice, and suggesting the priorities for clinical research in this field, an European Experts Panel took place in Avellino (Italy) in April 2003. Results and conclusions of that meeting are presented in this paper.
Notwithstanding the presence of the limitations described above, the panelists aimed for a consensus and to identify priorities for future research because of the clinical relevance of the issue.

Performance status as a prognostic factor

As in other types of cancer, PS has a clear prognostic role in advanced NSCLC. In all the retrospective and prospective trials regarding prognostic factors in this disease, PS has been shown to be an independent prognostic parameter [19–25]. In a series of more than 5000 patients with inoperable lung cancer analysed more than two decades ago to investigate the impact on survival of 50 prognostic factors, performance status, extent of disease and weight loss were among the most important prognostic factors [19]. These results have been confirmed by others [20–22, 25]. The survival analysis of 1960 patients with advanced NSCLC treated with cisplatin-based chemotherapy in five ECOG phase II or III trials conducted from 1981 to 1994 showed again an independent prognostic role of performance status: median survival was 9.4, 6.4 and 3.3 months in PS 0, 1 and 2 patients, respectively [25]. Median overall survival of patients with PS2—whatever the treatment under investigation—is always substantially shorter than that of PS0 or PS1 patients, and rarely exceeds 5 months [25–27], with 1-year survival rates <20%.

A worse PS is characterised by lower response rates to chemotherapy, shorter time to treatment failure and shorter progression-free survival [27, 28]. Chemotherapy also shows a reduced efficacy in PS2 patients when these patients receive a number of courses compared to patients with a better PS [29]. Moreover, it is a widely held opinion that these unfit patients are at higher risk for severe toxicity, which would counterbalance the eventual small benefit expected. The outcome of 64 PS2 patients enrolled in the clinical trial ECOG 1594 comparing four platinum-based combinations has been analysed in detail, after the accrual of PS2 patients had been stopped because of the perception of an excessive number of adverse events in this sub-group [27]. The study confirmed a substantial incidence of grade 3 and grade 4 toxicities in PS2 patients, although not significantly higher than in patients with better PS. The analysis of toxic deaths showed that only a part of the events were treatment-related and the remaining were secondary, at least in part, to the concomitant diseases often associated with an impaired PS. All these observations, as underlined by the authors, reinforce the perception that PS2 patients need special consideration when receiving chemotherapy.

Furthermore, the gross categories defined only by PS are inevitably heterogeneous: PS2 may be due to tumour-related symptoms (e.g., pain, anorexia, fatigue, weight loss), to concomitant diseases (e.g., smoking-related illnesses such as chronic obstructive pulmonary or cardiovascular disease, osteoarthritis, peripheral vascular disease, age-related decline in functional status) or both. For example, a 40-year-old PS2 patient confined to bed for a painful single bone metastasis is different from an elderly patient confined to bed for a moderate to severe cardiovascular co-morbidity. Different patients may have different benefit, different compliance and different toxicities from the same anti-cancer treatment. According to disease-related symptoms and pre-existing co-morbidities, patients could be divided in different sub-groups, with the aim of properly predicting risks and benefits of different therapeutic approaches. However, at present there is no validated categorisation of this type or prospective study assessing the real impact of different symptoms and co-morbidities on the risk/benefit ratio of chemotherapy. To date, the available data from retrospective analyses are few and heterogeneous, and do not allow any type of subclassification.

The role of chemotherapy in PS2 patients

A first point of discussion was the evidence supporting the role of chemotherapy itself in PS2 patients. The discouraging survival, the lower compliance to chemotherapy and the fear of a higher risk of toxicity put a question mark behind chemotherapy administration in this category of patients.

Some of the trials comparing best supportive care plus chemotherapy versus best supportive care alone are summarised in Table 2. In the meta-analysis published in 1995, although overall results were limited by statistical heterogeneity and evident outcome differences for the different chemotherapy categories, a significant benefit was demonstrated for cisplatin-based trials, and a sub-group analysis confirmed this benefit for both good and poorer PS patients [12]. After 1995, some advantage of chemotherapy versus supportive care alone has been shown not only with platinum-based combination chemotherapy [26, 29, 30] but also with many new cytotoxic agents (e.g. gemcitabine [31], vinorelbine [32], paclitaxel [33] and docetaxel [34]), administered as single agents. These drugs are usually characterised by a good tolerability, with a low incidence of severe adverse events. Most of the studies show some advantage of chemotherapy in terms of overall survival also in the sub-group of PS2 patients, although formal statistical comparisons are precluded by the low absolute number of patients. Disappointingly, data about QoL are scanty. Nearly all trials showed some benefit in terms of QoL and symptomatic improvement favouring chemotherapy against supportive care alone, but only one study [29] specifically analysed QoL in the different PS sub-groups. In that study, a comparison of mean baseline score with mean score after 6 weeks was planned. PS2 patients reported the worst scores at baseline assessment. The drop-out rate in PS2 patients was greater than in the other PS levels (35% compared with 23% in PS0 and 18% in PS1); thus, the analysis in this sub-group was limited to 31 patients out of 48 initially enrolled. Nevertheless, PS2 patients had significant benefit from chemotherapy and, with the greater potential for palliation determined by worse baseline condition, showed an improvement in QoL even higher than PS0 and PS1 patients.

When choosing between chemotherapy and supportive care alone, patients’ preferences should be taken into account, considering that most patients are willing to accept chemotherapy for a very small chance of benefit: patients with cancer are much more likely to opt for chemotherapy with minimal chance of benefit than people who do not have cancer, including medical and nursing professionals [35]. These findings should not be ignored, especially considering the availability of several drugs characterised by a favourable toxicity profile.
The role of adding platinum to third generation single agents in PS2 patients

At present, platinum-based combination chemotherapy is considered the standard treatment for advanced NSCLC, but it is still unclear if the benefit achieved with this treatment is restricted only to PS0 and PS1 patients, or also applies to PS2 patients. The results of a European phase III randomised trial comparing single-agent vinorelbine, vinorelbine–cisplatin and vindesine–cisplatin in 612 patients with advanced NSCLC and PS not worse than 2 were published in 1994 [6]. Cisplatin was administered at 120 mg/m² on days 1 and 29, and then every 6 weeks. The combination of cisplatin and vinorelbine was superior in terms of survival to vindesine–cisplatin and to vinorelbine alone. A subgroup analysis of that trial has been subsequently published, with the aim of testing interactions between treatments and main prognostic factors [36]. This secondary analysis showed that the significant advantage obtained with the combination of cisplatin and vinorelbine is predominantly limited to fit patients: in PS0–1 patients, median survival was 43, 36 and 33 weeks and 1-year survival was 38%, 34% and 29% for cisplatin–vinorelbine, vinorelbine alone and cisplatin–vindesine, respectively. In the sub-group of 120 PS2 patients enrolled in the trial (20%), instead, a median survival of 18 weeks, significantly lower than PS0-1 patients, was observed in all three arms. For PS2 patients, grade 3–4 haematological toxicity occurred earlier and more frequently in the arm receiving vinorelbine–cisplatin than in the vinorelbine arm (7 versus 28 days after the start of treatment, respectively). According to these results, cisplatin-based combination, with cisplatin doses higher than 100 mg/m², is no better than single-agent chemotherapy and should not be recommended to PS2 patients. Lower doses of cisplatin could probably be better tolerated, but currently there are no data supporting this hypothesis in PS2 patients.

As for the role of carboplatin, the results of the CALGB 9730 study, comparing paclitaxel plus carboplatin versus paclitaxel alone, must be considered [37]. The study enrolled patients with a PS of between 0 and 2. In the sub-group of PS2 patients (107 patients, 18% of the population), median survival in the group treated with combination chemotherapy was significantly longer than with paclitaxel alone (4.7 versus 2.4 months), with 18% and 10% of patients, respectively, alive at 1 year (log-rank, 0.0177; Wilcoxon, 0.0123). Similar to the benefit observed in the sub-group of elderly patients enrolled in the same trial, these results should be interpreted with caution, in view of the substantial risk of selection bias. Moreover, it should be noted that combination chemotherapy with carboplatin and paclitaxel produced a statistically significant higher incidence of several haematological and non-haematological severe toxicities (neutropenia, thrombocytopenia, anaemia, nausea and vomiting, any severe toxicity) than single-agent paclitaxel [37]. These data should of course be kept in mind when treating PS2 patients, who are at a higher risk of toxicity.

The role of non-platinum-based third generation polichemotherapy in PS2 patients

Fear of unacceptable toxicity is one of the major concerns in treatment decisions for PS2 patients and, from this point of view, platinum-free combination chemotherapy deserves attention as it is potentially less toxic than platinum-based treatment. In recent years, several trials comparing platinum-free combinations con-
taining new cytotoxic agents versus platinum-based treatment, enrolling patients with PS between 0 and 2, have been performed (Table 3) [38–42]. These trials are characterised by a remarkable heterogeneity among the drugs and schedules studied. As expected, platinum-based treatment is often associated with a higher occurrence of toxicity [38, 42]. Although a trend of slightly lower efficacy of combination chemotherapy without platinum is reported in some trials [40, 42], none of the trials show a statistically significant advantage for platinum-containing schedules. No significant interaction between treatment and PS in terms of overall survival is described, and platinum-free combination chemotherapy could represent a reasonable, less toxic option for PS2 patients.

However, there is no consistent evidence that combination chemotherapy without platinum is better than third generation drugs given as single agents. An Italian randomised trial compared the combination of gemcitabine and vinorelbine to the two single drugs in patients >70 years of age [9]. PS2 patients represented 18–19% in each of the three arms of the study. The primary analysis of the study showed that the combination was more toxic but it did not show advantage over mono-chemotherapy in terms of overall survival. Also in the sub-group of PS2 patients (130 patients), there was no advantage for combination chemotherapy over single agents (1-year survival was 20%, 18% and 22%, for vinorelbine, gemcitabine and the vinorelbine–gemcitabine combination, respectively). The hazard ratio of survival for combination chemotherapy was 1 when compared with vinorelbine and 0.97 when compared with gemcitabine.

**Role of new targeted agents**

In recent years, the rapidly expanding knowledge of cancer pathogenesis at a molecular level has provided new targets for drug discovery, and a great number of new anti-cancer drugs have been developed. Many of these biological agents are currently being tested, at different degrees of clinical development, in NSCLC.

Several features of target-based molecules make these drugs potentially ideal treatments for unfit patients. First, biological therapies hold the promise of being more selective and less toxic for normal tissues, both in terms of haematological and non-haematological adverse effects. Second, given a cytostatic rather than cytotoxic mechanism of action, these agents are more likely to be effective when they are administered continuously rather than in pulses, and oral formulations are preferred for continuous dosing schedules, with obvious logistic advantages for patients.

ZD1839, a small-molecule tyrosine-kinase inhibitor targeted against the epidermal growth factor receptor, is one of the most promising new biological agents. Its activity as second- or third-line therapy against NSCLC has been tested in two phase II trials, showing interesting response rates (from 10% to 20% in heavily pre-treated patients) and promising results in terms of symptom improvement (~40%) [43–46]. It is worth noting that this symptomatic improvement is usually obtained in a short time following the start of treatment and has also documented in PS2 patients. Unfortunately, however, no data on first-line treatments are currently available. New biological agents should be considered as excellent candidates for experimental treatments in clinical trials dedicated to PS2 patients, but as yet cannot be recommended in clinical practice.

**Consensus on clinical practice**

On the basis of current evidence, chemotherapy appears justified to patients with advanced NSCLC and a PS of 2 (Table 4). Subgroup analysis from several randomised trials suggest that several new generation cytotoxic drugs are superior to supportive care alone in this category of patients. Therefore, single-agent chemotherapy with these drugs (e.g. gemcitabine, vinorelbine, taxanes) could be the preferred option for palliative treatment of these patients. The choice of the drug should be based on the toxicity profile of each agent and type of co-morbid conditions. No data justify the use of platinum-free or high-dose (>100 mg/m²) cisplatin-based combination chemotherapy instead of single-agent treatment in PS2 patients. Although lacking specific data

### Table 3. Recent randomised trials of platinum-free versus platinum-based combination chemotherapy in advanced NSCLC

<table>
<thead>
<tr>
<th>Reference</th>
<th>P-based arm</th>
<th>P-free arm</th>
<th>Total No. of pts</th>
<th>Overall survival (months) (P-based versus P-free)</th>
<th>PS2 pts (% of total pts)</th>
<th>Outcome in PS2 patients (P-based versus P-free)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Georgoulis et al. [38]</td>
<td>CDDP/Doc</td>
<td>Gem/Doc</td>
<td>406</td>
<td>10 versus 9.5 (P = 0.98)</td>
<td>12</td>
<td>Comparable survival</td>
</tr>
<tr>
<td>Kosmidis et al. [39]</td>
<td>CBDCA/Ptx</td>
<td>Gem/Ptx</td>
<td>479</td>
<td>10.4 versus 9.8 (P = 0.32)</td>
<td>13</td>
<td>Comparable survival</td>
</tr>
<tr>
<td>Giaccone [40]</td>
<td>CDDP/Ptx (A) or CDDP/Gem (B)</td>
<td>Gem/Ptx</td>
<td>480</td>
<td>8.1 (A), 8.8 (B) versus 6.9 (P = NA)</td>
<td>12</td>
<td>Comparable survival</td>
</tr>
<tr>
<td>Alberola et al. [41]</td>
<td>CDDP/Gem (A) or CDDP/Gem/Vin (B)</td>
<td>Gem/Vin followed by Ifo/Vin</td>
<td>557</td>
<td>9.3 (A), 8.2 (B) versus 8.1 (P = NA)</td>
<td>15</td>
<td>NA</td>
</tr>
<tr>
<td>Gridelli et al. [42]</td>
<td>CDDP/Gem or CDDP/Vin</td>
<td>Gem/Vin</td>
<td>501</td>
<td>8.8 versus 7.4 (P = 0.08)</td>
<td>13</td>
<td>Comparable survival</td>
</tr>
</tbody>
</table>

P-based, platinum-based chemotherapy; P-free, platinum-free chemotherapy; PS, performance status; pts, patients; CDDP, cisplatin; Doc, docetaxel; Gem, gemcitabine; CBDCA, carboplatin; Ptx, paclitaxel; Vin, vinorelbine; Ifo, ifosfamide; NA, not available
in PS2 patients, the panellists considered combinations with cisplatin at lower doses ($\leq 100\text{ mg/m}^2$) as a possible treatment option. Taking into account the superiority shown by the carboplatin–paclitaxel combination compared to paclitaxel alone, even in PS2 patients, in one clinical trial [37], carboplatin-based doublets may also be considered as an alternative option in a selected sub-group of patients. Stronger evidence on the latter two points is expected from new clinical research specifically focused on PS2 patients affected by NSCLC.

**Consensus on clinical research**

All the panellists participating in the meeting agreed that an important prognostic and predictive help for clinical management could derive from a proper sub-classification of PS2 patients. However, it seems undeniable that the definition of prognostic sub-groups cannot be made in a subjective fashion and the only way to validate a prognostic score is to encourage and support prospective data collection.

As for treatment, the analysis of the available literature performed for this panel shows the absolute need for clinical trials specifically dedicated to PS2 patients. They represent a significant proportion of the patients that every oncologist has to manage in daily practice, and clinical decision making could be more strongly founded on the results of prospective studies. As in clinical research focused on elderly patients, in order to avoid selection bias, evidence should be based on clinical trials dedicated to these patients rather than on sub-group analysis coming from non-specifically designed trials [47]. The stringent exclusion criteria, the presence of co-morbidities, together with the subjective ‘feeling’ by the investigator that some PS2 patients could not tolerate the treatment under study, prevent a complete generalisability of the results obtained in the selected enrolled sub-group. Out of 43 ongoing phase II/III clinical trials for advanced NSCLC registered in the National Cancer Institute (NCI) Clinical Trials database at 30 April 2003 [48], information on PS eligibility was available for 37 trials: 18 trials were open to patients with PS from 0 to 2, 14 trials were limited to PS0–1 with the exclusion of PS2 patients, three trials were dedicated to unfit patients (elderly/poor PS) and only two were dedicated to PS2. These numbers show that in the last few years there has been a tendency to limit participation in randomised trials to fit patients, excluding PS2 patients. Such patients are eventually enrolled in clinical trials together with elderly patients and patients affected by major co-morbidities, under the common label of ‘special patient population’ or ‘patients unsuitable for platinum-based chemotherapy’. The panellists strongly disagree with this approach, which mixes together very different categories, leading to heterogeneous study populations. Elderly patients have peculiar characteristics related to physiological ageing with progressive reduction of organ functions and are at risk of unexpected and unpredictable toxicity. In our opinion, the differentiation of PS2 patients from elderly patients is mandatory for clear interpretation and to improve generalisability of trials’ results.

A consensus was reached that single-agent chemotherapy with one of the new agents (e.g. gemcitabine, vinorelbine or taxanes) should be the standard arm against which experimental treatments should be tested in randomised clinical trials dedicated to PS2 patients. There is an acceptable amount of data both in terms of survival and QoL (Table 2) which justifies the exclusion of best supportive care alone for further clinical studies in PS2 patients. Furthermore, there is an undeniable demand for specific treatment by patients and their relatives: patients are often much more willing to receive intensive treatments, even when clinicians forecast little benefit, if any [35]. In a descriptive study based on interviews asking for the preferences for chemotherapy in patients with advanced NSCLC, only 17% of the subjects would have accepted to be randomised between supportive care and chemotherapy [49].

Table 5 shows the most important research priorities for PS2 patients. High priority should be dedicated to prospective clinical trials evaluating tolerability and efficacy of platinum-based combinations (carboplatin-based or low-dose cisplatin-based doublets), as well as to trials testing the new biological target-oriented agents. Another interesting experimental field for these patients, taking into account the frequency of tumour-related symptoms, concomitant diseases and treatment side-effects, is the improvement of supportive care, with the aim to better define the role and the better schedule of administration of a wide spectrum of drugs (e.g. antidepressants, analgesics, haematological growth factors, etc.).

Regarding the choice of end points in clinical trials, it should be considered that symptomatic improvement is strongly requested

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**Table 4. Consensus on treatment of patients with advanced NSCLC and ECOG PS2 in clinical practice**

<table>
<thead>
<tr>
<th>Preferred option</th>
<th>Alternative options</th>
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<tr>
<td>Single-agent chemotherapy with a third generation drug (e.g. gemcitabine, vinorelbine, taxanes)</td>
<td>Carboplatin-based doublets</td>
</tr>
<tr>
<td>Cisplatin-based doublets with attenuated doses of cisplatin</td>
<td>Cisplatin-based doublets</td>
</tr>
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**Table 5. Research strategies in ECOG PS2 patients with advanced NSCLC**

<table>
<thead>
<tr>
<th>Hypothesis of experimental arm</th>
<th>Priority</th>
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<tbody>
<tr>
<td>Investigational agent (e.g. pemetrexed, oral formulations)</td>
<td>Medium</td>
</tr>
<tr>
<td>Alternative dose and/or scheduling of single agents</td>
<td>Medium/high</td>
</tr>
<tr>
<td>Carboplatin- or low dose cisplatin-based combination</td>
<td>High</td>
</tr>
<tr>
<td>Biological target-based agent without chemotherapy</td>
<td>High</td>
</tr>
<tr>
<td>Supportive treatment added to chemotherapy</td>
<td>Medium</td>
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by the patients. When patients with advanced NSCLC, who had already experienced a cisplatin-based chemotherapy, were asked about the benefit thresholds to accept chemotherapy, only 22% of patients with advanced NSCLC would have chosen chemotherapy over best supportive care when a 3-month improvement in survival was hypothesised, whilst a much larger proportion (68%) chose chemotherapy if it significantly reduced symptoms, even though not prolonging survival [49]. Although a substantial improvement in overall survival should obviously be the ideal aim of clinical research, considering the very poor prognosis of PS2 patients irrespective of the treatment administered, patient-related end points other than overall survival (symptom relief, clinical benefit, health-related QoL) should play a central role in the planning, conducting and analysing of trials dedicated to PS2 patients.

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References


