EORTC Elderly Task Force and Lung Cancer Group and International Society for Geriatric Oncology (SIOG) experts’ opinion for the treatment of non-small-cell lung cancer in an elderly population

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Non-small-cell lung cancer (NSCLC) represents a common health issue in the elderly population. Nevertheless, the paucity of large, well-conducted prospective trials makes it difficult to provide evidence-based clinical recommendations for these patients. The present paper reviews the currently available evidence regarding treatment of all stages of NSCLC in elderly patients. Surgery remains the standard for early-stage disease, though pneumonectomy is associated with higher incidence of postoperative mortality in elderly patients. Given the lack of demonstrated benefit for the use of adjuvant radiotherapy, it is also not recommended in elderly patients. Elderly patients seem to derive the same benefit from adjuvant chemotherapy as younger patients do, with no significant increase in toxicity. For locally advanced NSCLC, concurrent chemoradiotherapy may be offered to selected elderly patients as there is a higher risk for toxicity reported in the elderly population. Third-generation single-agent treatment is considered the standard of care for patients with advanced/metastatic disease. Platinum-based combination chemotherapy needs to be evaluated in prospective trials. Unfortunately, with the exception of advanced/metastatic NSCLC, prospective elderly-specific NSCLC trials are lacking and the majority of recommendations made are based on retrospective data, which might suffer from selection bias. Prospective elderly-specific trials are needed.

Key words: age, elderly, experts’ opinion, EORTC, lung cancer, NSCLC, SIOG

introduction

Non-small-cell lung cancer (NSCLC) remains the leading cause of cancer-related death in both men and women in Western countries, representing the 80% of lung cancer cases [1].

As a result of an increasing life expectancy, the incidence of lung cancer diagnosed in the elderly population is rising. About 50% of newly diagnosed NSCLC cases occur in patients aged >65 years, while 30%–40% of cases are diagnosed in patients aged >70 years [2]. Data from the Surveillance, Epidemiology, and End Results (SEER) registry indicate that the median age at diagnosis in NSCLC patients is 69 years [3]. Based on these observations, it is clear that NSCLC represents a significant health problem in elderly.

The cut-off point at which an adult is considered ‘elderly’ has not been well defined. Usually, age 70 years is considered a reference point and is commonly used in clinical trials in oncology [4]. Based on available literature, especially at or around 70 years of age, a number of age-related physiologic changes occur, which increase the risk of toxicity related to systemic therapy; hence age 70 is widely accepted as cut-off for elderly-specific analyses [4].

Despite the high frequency of NSCLC in the elderly population, elderly patients are frequently underrepresented in clinical trials evaluating new cancer treatments [5]. Indeed, statistically significant underrepresentation of the elderly was noted in registration trials for all cancer treatment except for breast cancer hormonal therapies, and this underrepresentation was more pronounced for patients aged ≥70 years [6]. As a result, it is difficult to reach evidence-based clinical recommendations, which apply to the treatment of the elderly. Consequently, the elderly are often undertreated or receive therapies that have not been tested in relevant clinical trials. Furthermore, the likelihood of receiving any kind of treatment of NSCLC, particularly chemotherapy, decreases significantly with age [7–10]. Potential explanations for this scenario are the belief that elderly patients are in general incapable of tolerating
the treatment-related toxic effects and in addition the expectations for long-term benefits are limited not only on the part of physicians but also on the patients or their families. A systematic review of barriers to the recruitment of older patients to cancer clinical trials revealed barriers related to cancer trial design (e.g. protocol eligibility criteria with restrictions on comorbid conditions or organ function requirements to optimize treatment tolerability) and individual physicians skepticism (e.g. the perception that the patient would not be able to tolerate treatment due to comorbidities and advanced age) [11]. Furthermore, patient-related barriers have also been reported, such as difficulty in accessing university hospitals, lack of adequate information about the availability of clinical trials and the need to obtain their treating physician’s endorsement to participate in a clinical trial [12, 13].

The purpose of this review was to focus on insights to optimize treatments for NSCLC in the elderly population. Proper integration of various modalities, i.e. surgery, radiotherapy (RT), chemotherapy and targeted therapy for all stages of NSCLC will be the key.

search strategy and selection criteria

A bibliographic search of the Medline database was conducted for papers published from 1 January 1998 to 1 October 2008, with the keywords ‘non-small-cell lung cancer’, ‘elderly’, ‘surgery’, ‘chemotherapy’ and ‘radiotherapy’. The search was limited to articles written in English. Studies with subgroup analysis of treatment efficacy for elderly patients and retrospective analyses comparing elderly patients with non-elderly counterparts were included. When considering chemotherapy, RT or multimodality treatment, only data from phase III trials or randomized phase II trials were incorporated. The Medline search was supplemented by a manual search of meeting abstracts [World Conference on Lung Cancer, European Society of Medical Oncology Annual Congress, American Society of Clinical Oncology (ASCO) Annual Meeting and European Lung Cancer Conference] as well as reference lists of original and review articles. A consensus was reached among all authors for the recommendations. We did not use the level of evidence and grade of recommendation according to ASCO guidelines because age cut-offs varied and most studies consisted of subgroup age-specific analyses.

results

Early-stage NSCLC: Surgery: The literature search revealed 24 papers concerning surgical series in elderly NSCLC patients. Adjuvant chemotherapy/RT: Two papers addressed adjuvant chemotherapy (a retrospective subgroup analysis of a phase III study and a pooled analysis of the effect of age on adjuvant chemotherapy). There were no papers on postoperative adjuvant RT while six studies dealt with the issue of radical RT for potentially resectable tumors. Locally advanced NSCLC: Regarding locally advanced NSCLC, one prospective phase III elderly-specific trial and eight retrospective age-specific subanalyses were included. Metastatic NSCLC: For first- and second-line treatment of advanced/metastatic NSCLC, there were 14 retrospective subgroup analyses (9 full papers and 5 in abstract form) and 6 prospective randomized phase II and III studies. In these prospective studies, comparisons included single-agent chemotherapy versus best supportive care (BSC), different treatment regimens of single-agent chemotherapy, single-agent versus doublet and single-agent chemotherapy versus targeted agents.

early stage surgery. Surgery is the primary treatment of choice for stages I, II and some subsets of stage IIIA NSCLC. The role of surgery in the elderly has significantly changed during the last 15 years. During the 1980s, age was considered a relative contraindication to thoracotomy, and surgical intervention in the elderly was approached with a great deal of hesitation. Nevertheless, advances in anesthetic management and surgical techniques allowed the inclusion increasing numbers of the elderly patients in surgical studies. In spite of this, age still appears to be a major factor influencing treatment choice and curative cancer-directed surgery is often omitted in elderly patients [8, 14, 15]. Several studies support that the surgical treatment of NSCLC in the elderly is feasible and that age per se is not a contraindication for various surgical procedures (Table 1) [16–40]. It should be underscored that these are retrospective studies and highly susceptible to selection bias.

There are two substantial issues regarding surgical treatment of NSCLC in the elderly population. The first one concerns the outcome, namely the survival of elderly patients undergoing surgery for NSCLC. Several publications over the years have supported the view that patient age is not a negative prognostic factor for long-term postoperative survival. Five-year survival rates range between 21% and 58% depending on the stage of patients included in the study [16–21, 23–26, 28–39]. Moreover, studies comparing outcomes between elderly versus younger patients have not demonstrated significant differences in overall survival (OS) [17, 24, 26, 28, 31, 40] or change in functional status [33]. Furthermore, a recent study reports a significantly higher 5-year survival for elderly versus younger patients with stage I NSCLC [31]. Nevertheless, this was not the case in two studies reported by Kamiyoshihara et al. [22] and Mery et al. [27]. The former study reported significantly higher 5- and 10-year OS rates for younger patients [22]. Nevertheless, when cancer-specific survival was considered, there was no significant difference between the two groups, clearly underlining the importance of taking into account the issue of cancer-unrelated deaths, when evaluating survival in elderly cancer patients. The second study reported age as a significant predictor of both overall and cancer-related survival, with the elderly having consistently lower survival [27]. A possible explanation for this observation is the type of surgery carried out in the elderly patients. More often than not, the surgical procedure is palliative or a limited resection is the end result, although the authors assert that the type of surgery cannot completely explain the differences in survival observed between age groups [27]. Another retrospective analysis of all patients diagnosed with NSCLC between 1995 and 1999 in the Netherlands supported that age was an independent prognostic factor for patients with localized disease [14]. Nevertheless, the
authors included all patients in the evaluation of survival, even those often elderly who had not been subjected to a surgical procedure, and furthermore, cancer-related survival was not reported. Moreover, another large retrospective study from the Netherlands, by van Rens et al., which assessed 2361 patients with NSCLC, reported that patients aged ≥65 years had significantly shorter 5-year OS when compared with patients <65 years old (young 44% versus elderly 38%, \( P < 0.001 \)) [41]. The authors also reported that the 4-year OS was very similar (young 48% versus elderly 44%, \( P = \) nonsignificant) and that

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Age (years)</th>
<th>Stage</th>
<th>5-year survival (%)</th>
<th>Morbidity (%)</th>
<th>Mortality (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciriaco et al. [16]</td>
<td>76</td>
<td>≥70</td>
<td>I–IIIA</td>
<td>53 (54-month actuarial survival)</td>
<td>19.7</td>
<td>1.3</td>
</tr>
<tr>
<td>Hanagiri et al. [17]</td>
<td>18</td>
<td>280</td>
<td>I–IIIA</td>
<td>42.6</td>
<td>50</td>
<td>0</td>
</tr>
<tr>
<td>Thomas et al. [18]</td>
<td>500</td>
<td>≥70</td>
<td>I–IIIA</td>
<td>34</td>
<td>NR</td>
<td>7</td>
</tr>
<tr>
<td>Pagni et al. [19]</td>
<td>385</td>
<td>≥70</td>
<td>NR</td>
<td>NR</td>
<td>34</td>
<td>4.2</td>
</tr>
<tr>
<td>Oliaro et al. [20]</td>
<td>258</td>
<td>≥70</td>
<td>I–IIIA</td>
<td>Stage I: 73.6 Stage II: 23 Stage IIIA: 8.9</td>
<td>39.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Sioris et al. [21]</td>
<td>75</td>
<td>275</td>
<td>I–IIIA</td>
<td>32</td>
<td>29</td>
<td>9</td>
</tr>
<tr>
<td>Kamiyoshihara et al. [22]</td>
<td>37</td>
<td>≥70</td>
<td>NR</td>
<td>35.1</td>
<td>NR</td>
<td>0</td>
</tr>
<tr>
<td>Conti et al. [23]</td>
<td>151</td>
<td>≥70</td>
<td>I–IV</td>
<td>40% (4-year actuarial survival)</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>Yamamoto et al. [24]</td>
<td>132</td>
<td>≥70</td>
<td>I</td>
<td>58.23</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Birim et al. [25]</td>
<td>126</td>
<td>≥70</td>
<td>I–IV (postsurgery pathological staging)</td>
<td>37</td>
<td>13 (major complications)</td>
<td>3.2</td>
</tr>
<tr>
<td>Sawada et al. [26]</td>
<td>66</td>
<td>≥70</td>
<td>I–IV (postsurgery pathological staging)</td>
<td>NR</td>
<td>57 (minor complications)</td>
<td>4.1</td>
</tr>
<tr>
<td>Mery et al. [27]</td>
<td>2382</td>
<td>≥75</td>
<td>I–II</td>
<td>Median survival 28 months</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Yazgan et al. [28]</td>
<td>30</td>
<td>≥70</td>
<td>NR</td>
<td>21.3</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Muraoka et al. [29]</td>
<td>33</td>
<td>≥80</td>
<td>I–II</td>
<td>Median survival ND:26 ND0: 76 ND0: 23</td>
<td>ND: 45</td>
<td>0 for both groups</td>
</tr>
<tr>
<td>Matsuoka et al. [30]</td>
<td>40</td>
<td>≥80</td>
<td>I–IIIA</td>
<td>56.9</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Cerfolio and Bryant [31]</td>
<td>726</td>
<td>≥70</td>
<td>I–IV</td>
<td>51</td>
<td>20</td>
<td>2.2</td>
</tr>
<tr>
<td>Dominguez-Ventura et al. [32]</td>
<td>294</td>
<td>≥80</td>
<td>I–IIIB</td>
<td>3</td>
<td>48</td>
<td>6.3</td>
</tr>
<tr>
<td>Sullivan et al. [33]</td>
<td>25</td>
<td>≥70</td>
<td>I–II</td>
<td>NR</td>
<td>48</td>
<td>0</td>
</tr>
<tr>
<td>Sirbu et al. [34]</td>
<td>273</td>
<td>≥70</td>
<td>I–IV (postsurgery pathological staging)</td>
<td>35.6</td>
<td>48</td>
<td>5.4</td>
</tr>
<tr>
<td>Dyszkiewicz et al. [35]</td>
<td>90</td>
<td>≥70</td>
<td>I–IV</td>
<td>NR</td>
<td>78.5 (pneumonectomy)</td>
<td>16.6 (pneumonectomy)</td>
</tr>
<tr>
<td>Aoki et al. [36]</td>
<td>35</td>
<td>≥80</td>
<td>I–IIIB</td>
<td>39.8</td>
<td>60</td>
<td>0</td>
</tr>
<tr>
<td>Brock et al. [37]</td>
<td>68</td>
<td>≥80</td>
<td>I–IV (postsurgery staging)</td>
<td>34</td>
<td>44</td>
<td>8.8</td>
</tr>
<tr>
<td>Port et al. [38]</td>
<td>61</td>
<td>≥80</td>
<td>I–IIIA</td>
<td>38</td>
<td>38</td>
<td>1.6</td>
</tr>
<tr>
<td>Spaggiari and Scanagatta [39]</td>
<td>145</td>
<td>≥75</td>
<td>I–IV</td>
<td>49.8</td>
<td>11</td>
<td>0.6</td>
</tr>
</tbody>
</table>

NR, not reported; ND, lymph node dissection; ND0, no lymph node dissection.
the survival difference was only observed in subgroups of patients with good prognosis. These observations imply that the increased mortality in the elderly was due to advancing age and comorbidities, although cancer-specific mortality was not reported [41].

The second important issue relates to the complications observed with treatment, namely postoperative morbidity and mortality. Regarding morbidity, published results are conflicting: some studies support an association between increased age and occurrence of postoperative complications [28], while others do not [19, 31]. Although postoperative morbidity has a significant impact on patient quality of life (QoL), postoperative mortality is considered to be the more critical outcome. The literature is similarly divided regarding postoperative mortality. A number of studies report a higher incidence of fatal complications in elderly patients [18, 34, 42], while several other studies do not confirm this observation [17, 22, 31, 33]. A large Norwegian population-based study, with 3224 NSCLC patients treated by surgery, reported higher postoperative mortality with advancing age, especially after pneumonectomy [43].

A consistent observation reported by several studies is that a significant parameter for postoperative complications is the presence of comorbidities, primarily lung or heart diseases [18, 25, 34, 35, 44, 45]. Preoperative selection based on cardiac evaluation studies and assessment of pulmonary function are required in order to further improve results [39].

The extent of surgery also impacts postoperative morbidity and mortality. The Lung Cancer Study Group concluded that lobectomy is a superior operation for T1N0 NSCLC based on a randomized trial of lobectomy versus more limited resection [46]. Nevertheless, some retrospective data support a more limited operation for elderly patients [27, 39]. Nevertheless, there is not enough data to indicate the use of limited resections in every elderly patient with early NSCLC [45]. As a number of surgical series in elderly patients report higher postpneumonectomy mortality [18–21, 34, 35, 47], age should be a parameter when deciding whether a patient is suitable for pneumonectomy [39, 45, 48].

During the 1990s, video-assisted thoracoscopic surgery (VATS) emerged as a minimally invasive surgical technique. VATS is associated with reduced postoperative morbidity and shorter hospital stay compared with open procedures [49]. VATS has been evaluated in elderly population by several groups, with encouraging results, even in octogenarians [50–53], with postoperative morbidity of 15%–41% and postoperative mortality of <2%. McVay et al. reported a series of 159 lung cancer patients aged ≥80 years (range 80–94) treated with VATS, with very low postoperative morbidity (18%) and mortality (1.8%) [52]. Igai et al. reported the results of 95 octogenarians treated with either VATS (n = 58) or the standard thoracotomy (n = 37). Postoperative cardiopulmonary complications were observed more frequently in the standard thoracotomy group (P = 0.03). The overall 5-year survival for the whole group was 54.4% [33]. Nevertheless, given the small number of patients, the small number of studies and their retrospective nature, no firm recommendations can be made and these results must be further confirmed in elderly-specific prospective trials. It is safe to say that VATS can be applied to the elderly and the results are comparable with those seen to the younger patients.

**recommendation.** Surgical options should not be discarded for elderly patients based solely on their chronological age. Tumor stage, patient life expectancy, performance status (PS) and the presence of comorbidities should be taken into account when deciding to treat or not treat an elderly patient with surgery. Whether elderly patients should be offered lobectomy as a ‘standard of care’ or more limited procedures (i.e. wedge resection) is not clear, although retrospective data indicate that both these procedures yield similar outcomes. Pneumonectomy should be avoided or carried out with caution, given the higher rate of mortality reported with this procedure. Careful patient selection with preoperative evaluation based on cardiac and respiratory assessment is mandatory and could significantly improve the results.

**adjuvant chemotherapy after surgical resection.** The recent data from randomized adjuvant clinical trials [54–56] as well as from a recent meta-analysis [57] have changed the standard of care for patients with completely resected NSCLC. Adjuvant cisplatin-based chemotherapy is associated with a significant survival benefit, with a 5.3% absolute increase in 5-year OS, in favor of adjuvant chemotherapy compared with no further treatment [57].

A pooled analysis of the effect of age on outcome after adjuvant cisplatin-based chemotherapy was recently reported [58]. This analysis considered individual patient data from five randomized trials [54–56, 59, 60], with 4584 patients registered in the lung adjuvant cisplatin analysis database [57]. Outcome and toxicity data were compared between three age groups <65 (n = 3269, 71%), 65–69 (n = 901, 20%) and ≥70 (n = 414, 9%). Elderly patients (aged ≥70 years) received significantly lower total doses of cisplatin when compared with younger patients (P < 0.0001) and significantly lower number of chemotherapy cycles (P < 0.0001); however, the survival benefit from cisplatin adjuvant chemotherapy was not different according to age group. No significant difference was observed regarding toxicity and more elderly patients died from noncancer-related causes (P < 0.0001) [58].

A retrospective subgroup analysis for elderly population of a randomized phase III trial (National Cancer Institute of Canada and Intergroup Study JBR.10) of adjuvant chemotherapy versus observation [55] was recently reported [61]. The cut-off point for elderly in this retrospective analysis was set at 65 years. The chemotherapy regimen used in JBR.10 was vinorelbine and cisplatin. Although more elderly patients had poor PS at baseline, a similar outcome in terms of OS was observed for young and elderly patients [hazard ratio (HR) for young versus elderly 0.77; 95% confidence interval (CI) 0.57 to 1.03; P = 0.08], and only patients >75 years old had a HR of 2.41 (95% CI 1.43 to 4.06; P < 0.001). Similarly, no significant difference was observed regarding disease-specific survival (DSS) (HR for young versus elderly 0.88; 95% CI 0.63 to 1.21; P = 0.45). OS and DSS were also evaluated in all elderly patients by randomized treatment group. There was a survival benefit in favor of chemotherapy in elderly patients (HR 0.61; P = 0.04) that was similar to the treatment effect in the overall trial population. Toxic effects observed were similar between the two
groups. Treatment effect was also assessed to patients aged >75 years, although there were only 12 assessable patients in the chemotherapy arm and 11 in the observation arm. Chemotherapy effect in this subgroup (HR 2.35; 95% CI 0.84 to 6.58; \(P = 0.09\)) was significantly different from that of the whole cohort (\(P = 0.03\) for chemotherapy by age >75 years interaction). Similar results were observed in DSS for the subgroup (HR 7.13; 95% CI 0.85 to 60.00; \(P = 0.04\); for chemotherapy by age >75 years interaction). Elderly patients received fewer chemotherapy doses when compared with younger counterparts and had lower dose intensities for both drugs. Nevertheless, toxicity data analysis support that this was not due to a higher incidence of adverse events in elderly population. More elderly patients discontinued chemotherapy treatment due to refusal compared with younger patients. Prospective comparative trials using modified and better tolerated regimens carried out specifically in the elderly are clearly warranted.

**recommendation.** Despite receiving a lower total chemotherapy dose, elderly patients seem to derive the same benefit from adjuvant chemotherapy as younger patients do, with no significant increase in toxicity. Given this, adjuvant chemotherapy should not be denied to patients on the basis of age. Treatment decisions should take into account the estimated absolute benefit, life expectancy, treatment tolerance, cognition, presence of comorbidities and patient preferences. Less information is available regarding the real benefit and tolerability of these regimens for patients aged >75 years and the risk versus benefit has not been studied adequately. It should be noted that these are retrospective data based on highly selected patients and their extrapolation to the general elderly population should be made with caution.

**adjuvant RT after surgical excision.** The role of adjuvant RT after surgical resection in the treatment of NSCLC remains uncertain. The post-operative radiotherapy (PORT) meta-analysis [62, 63] included information on 2128 patients and reported that postoperative RT had a detrimental effect on survival, which was more pronounced for patients with lower nodal status. Nevertheless, the PORT meta-analysis has been criticized for its long enrollment period and use of different types of machines, techniques and doses. Three trials have been published after the PORT meta-analysis, all failing to support a general benefit for the use of postoperative RT [64–66].

Regarding patients with stage III/N2 disease, neither the PORT meta-analysis nor the subsequently published trials found an adverse effect of RT in connection with survival [62–66]. A retrospective analysis of the N2-positive subgroup demonstrated higher survival of those patients who had received postoperative RT [56]. On the basis of these results, routine postoperative RT is not recommended for patients with completely resected stage I–III A NSCLC [67, 68].

**radical RT for potentially resectable tumors.** Although advances in anesthetic management and surgical techniques have increased the percentage of elderly patients undergoing surgical operations for NSCLC, some never undergo surgery. Common reasons for not undergoing surgery are older age, presence of serious comorbidities and patient’s refusal. For those elderly patients with early-stage NSCLC who do not undergo an operation, RT can be administered with curative intent, albeit with lower survival rates when compared with surgery [69]. Several studies have demonstrated that RT with curative intent is feasible and tolerable in the elderly population with NSCLC [70–75]. Furthermore, when elderly patients were compared with the younger subgroup, no significant differences were reported in terms of recurrence-free survival [72] or OS [72, 73]. In the largest series reported by Pignon et al. [75], 1208 NSCLC patients were included. No significant survival difference was observed between patients aged <65, 65–70 and >70 years. Although no differences regarding toxicity were observed, more elderly patients experienced weight loss than their younger counterparts [75]. Newer techniques of radiation like three-dimensional conformal RT, intensity-modulated radiation therapy, stereotactic body RT, and particle beam RT need to be explored in the elderly patients [76]. Several reports have shown that stereotactic body radiation is a safe and effective method of treating lung cancer in medically inoperable patients, with survival rates potentially comparable to those of surgery [77, 78]. Because it is more easily tolerated, stereotactic body radiation therapy might be of particular interest in the elderly [79].

**recommendation.** There is nearly a complete lack of data, both prospective and retrospective, regarding the role of postoperative adjuvant RT, especially for elderly NSCLC populations. Given the lack of demonstrated benefit for the use of RT in the general population, adjuvant RT is also not recommended for elderly NSCLC patients. When used with curative intent in elderly patients not suitable for surgery, RT is well tolerated and older and younger patients benefit in a similar way.

**locally advanced**

Concurrent chemoradiotherapy (CMRT) is considered the standard therapy for unresectable stage III NSCLC. In several trials, concurrent administration of platinum-based chemotherapy with RT has been demonstrated to confer a modest but statistically significant survival benefit compared with sequential administration, with median survival times of 15–17 months for concurrent therapy versus 12.9–14.6 months for sequential administration [80–83]. Nevertheless, according to ASCO guidelines, concurrent CMRT should only be considered for patients with good PS [84]. In the clinical setting, concurrent CMRT is associated with significant toxic effects including esophagitis, risk for radiation pneumonitis and increased myelosuppression. Data from the SEER database show that most elderly patients not receive combined modality treatment [85]. This reflects the uncertainty about concurrent CMRT as a treatment of choice for elderly patients with locally advanced NSCLC.

One phase III elderly-specific trial has evaluated CMRT versus RT alone [86]. Patients were randomly assigned to RT (60 Gy) alone or to the CMRT arm (same RT with concurrent use of carboplatin 30 mg/m2). The study was prematurely closed after enrollment of only 46 of the 190 originally planned patients (23 in the RT arm and 23 in the CMRT arm) because four treatment-related deaths occurred (three in the CMRT
arm; two deaths were considered due to pneumonitis). At that time, OS was 428 days on the RT arm versus 554 days on the CMRT arm. Unfortunately, because of its premature closure and the small number of patients randomized, no definitive conclusions can be drawn from this study.

Some studies that provided retrospective subgroup analysis for age as prognostic factor in CMRT trials could not identify age as a negative prognostic factor [80], while others did [87, 88].

The Radiation Therapy Oncology Group (RTOG) pooled together the results of 749 NSCLC patients participating on three separate RTOG trials. These patients had received RT alone; hyperfractionated RT (hRT); induction platinum-based therapy, followed by either RT alone or concurrent CMRT or concurrent CMRT with hRT. One hundred fourteen patients (15%) were ≥70 years of age. The authors reported that as therapy intensified, the incidence of grades 3–5 toxic effects increased in elderly population. They found no significant difference in survival between treatment arms in these elderly patients. The conclusion was that unlike the overall patient population, elderly patients did not benefit from increased therapeutic intensity and that sequential or concurrent CMRT showed less, if any, benefit over RT alone for elderly patients [89].

Four other studies reported the results of age-based retrospective subgroup analyses of randomized phase III trials, which evaluated concurrent CMRT in one arm [90–93]. All four studies concluded that elderly and younger patients derive similar survival benefit from CMRT (Table 2) but also found that there is a significantly greater risk of short-term hematologic and nonhematologic toxicity for elderly patients, which may outweigh the observed benefit. Furthermore, the evidence from retrospective trials could suffer from selection bias and the conclusions may not be representative of the whole elderly population, but only of patients considered eligible for such an aggressive treatment as CMRT [94].

**Recommendation.** Concurrent CMRT approach should be offered to elderly patients with locally advanced NSCLC. Nevertheless, given the lack of prospective randomized trials, specifically designed for the elderly population, and given the higher risk of toxicity in elderly patients, treatment decision should be based on PS, absence of significant comorbid diseases and patient life expectancy. Trials specifically designed for the elderly population are urgently needed and patients should be encouraged to participate in such clinical trials.

### advanced/metastatic

#### single-agent chemotherapy versus BSC

The question of single-agent chemotherapy versus BSC in elderly patients with advanced/metastatic NSCLC was investigated by the Italian phase III trial, Elderly Lung Cancer Vinorelbine Italian Group Study (ELVIS) [95]. This trial included 154 patients ≥70 years old who were randomly assigned to BSC or vinorelbine 30 mg/m² on days 1 and 8. After a median follow-up of 57 weeks, the study clearly demonstrated that there was a significant survival advantage in favor of the vinorelbine arm \((P = 0.03)\); median survival was 21 weeks for BSC versus 28 weeks for vinorelbine;

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Hematologic toxicity</th>
<th>Nonhematologic toxicity</th>
<th>Median OS(^a) (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lager et al. [90]</td>
<td></td>
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</tr>
<tr>
<td>&lt;70 years old</td>
<td>491</td>
<td>Higher grade (\geq 3) neutropenia for the elderly patients</td>
<td>23% (CMT-RT); 42% (CMT-hRT)</td>
<td>10.8 (sequential arm)</td>
</tr>
<tr>
<td>≥70 years old</td>
<td>104</td>
<td></td>
<td>33% (CMT-RT); 60% (CMT-hRT)</td>
<td>16.4 (CMT-hRT)</td>
</tr>
<tr>
<td>Rocha-Lima et al. [91]</td>
<td></td>
<td>Grade (\geq 3)</td>
<td>Grade (\geq 3)</td>
<td></td>
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<tr>
<td>&lt;50</td>
<td>22</td>
<td>65%</td>
<td>0%</td>
<td>10.9</td>
</tr>
<tr>
<td>50–59 years old</td>
<td>77</td>
<td>71%</td>
<td>0%</td>
<td>12.7</td>
</tr>
<tr>
<td>60–69 years old</td>
<td>123</td>
<td>84%</td>
<td>6%</td>
<td>15.4</td>
</tr>
<tr>
<td>≥70 years old</td>
<td>31</td>
<td>83% (P = 0.028)</td>
<td>11% (P = 0.0025)</td>
<td>13.4</td>
</tr>
<tr>
<td>Schild et al. [92]</td>
<td></td>
<td>Grade (\geq 4)</td>
<td>Grade (\geq 4) 5-year survival</td>
<td></td>
</tr>
<tr>
<td>&lt;70 years old</td>
<td>181</td>
<td>56%</td>
<td>1%</td>
<td>18%</td>
</tr>
<tr>
<td>≥70 years old</td>
<td>63</td>
<td>78% (P = 0.003)</td>
<td>6% (P = 0.02)</td>
<td>13%</td>
</tr>
<tr>
<td>Sgroi et al. [93]</td>
<td></td>
<td>Elderly patients more likely to discontinue treatment due to toxicity (12% versus 2%)</td>
<td>Higher incidence of esophagitis (23% versus 15%) and dehydration (15% versus 7%) in elderly patients</td>
<td>21.2 (P = 0.3255)</td>
</tr>
</tbody>
</table>

\(^a\)For patients ≥70 years old.

\(^b\)Renal toxicity.

\(^c\)Pneumonitis.

CMT-RT, concurrent chemotherapy-conventional RT; CMT-hRT, concurrent chemotherapy-hyperfractionated RT.
survival rates at 6 and 12 months in the control arm were 41% and 14%, respectively, versus 55% and 32%, respectively, in the vinorelbine arm. Only five patients discontinued treatment because of toxicity and there were no treatment-related deaths. Treatment with vinorelbine also resulted in significant improvement in terms of QoL.

choice of single-agent chemotherapy. Based on the results of the ELVIS trial, subsequent trials tried to determine which single agent is best for the treatment of elderly patients. A recently reported phase III trial compared docetaxel (60 mg/m², on day 1, every 21 days) with vinorelbine (25 mg/m², on days 1 and 8, every 21 days) in 182 NSCLC patients aged ≥70 years [96]. Median OS, which was the study’s primary end point, was not significantly different between two arms. Nevertheless, it should be underlined that this trial was underpowered to show a survival difference and there was a trend toward higher survival in favor of docetaxel (14.3 versus 9.9 months; \( P = 0.138 \)). All other outcome measures, specifically progression-free survival (PFS) (5.5 versus 3.1 months; \( P < 0.001 \)), response rate (22.7% versus 9.9%; \( P = 0.019 \)) and disease-related symptoms were significantly resolved with docetaxel when compared with vinorelbine. Adverse events were similar between the two agents with the exception of neutropenia, which was more common with docetaxel (83% for docetaxel; 69% for vinorelbine; \( P = 0.03 \)). This study established a role for docetaxel as monotherapy for elderly patients with advanced-stage NSCLC.

single agent versus non-platinum-based doublet. Two prospective randomized phase III trials evaluated whether combination regimens offer further benefit over monotherapy for elderly NSCLC patients. Nevertheless, published results are conflicting and it is not clear whether combination therapy offers any benefit compared with monotherapy.

The South Italian Cooperative Oncology Group (SICOG) reported the results of a phase III trial of vinorelbine (30 mg/m²; days 1 and 8, every 21 days) versus vinorelbine/gemcitabine doublet (vinorelbine: 30 mg/m²; gemcitabine 1200 mg/m²; both drugs on days 1 and 8, every 21 days) [97, 98]. The estimated sample size was 120 patients per arm, but a preplanned interim analysis of survival was done when the first 60 patients were enrolled per arm. The study was prematurely terminated when results from the interim analysis yielded a significant survival benefit for the combination arm (median OS: 29 weeks) versus the single-agent arm (median OS: 18 weeks). The estimated 6-month and 1-year survival rates were 56% and 30% in the combination arm compared with 32% and 13% in the single-agent arm (\( P < 0.01 \)). In multivariate Cox analysis, after adjustment for stage of disease, Eastern Cooperative Oncology Group (ECOG) PS, histology, Charlson score and weight loss, the risk of death in the combination arm compared with the single-agent arm was 0.48 (95% CI 0.29 to 0.79; \( P < 0.01 \)). Symptom and QoL deterioration was more likely to occur in the monotherapy arm (6 months without symptom and QoL deterioration: 43% versus 22% in the combination and single-agent arms, respectively). No significant differences regarding toxicity were observed between the two groups.

Nevertheless, a much bigger phase III trial reported conflicting results. The Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III trial [99] compared either vinorelbine (30 mg/m²) or gemcitabine (1200 mg/m²), both drugs given on days 1 and 8, to a vinorelbine/gemcitabine doublet (vinorelbine: 25 mg/m²; gemcitabine 1000 mg/m²; both drugs on days 1 and 8). Of 698 patients ≥70 years old available for intention-to-treat analysis, 233 were assigned to receive vinorelbine, 233 gemcitabine and 232 vinorelbine plus gemcitabine. There was no difference between each single-agent and the combination arm in terms of PFS and OS. Median OS was 36 and 28 weeks for vinorelbine and gemcitabine single agent, respectively; estimated 1-year survival was 38% and 28% for patients in the vinorelbine and gemcitabine arms, respectively. For patients in the combination arm, median survival was 30 weeks, with an estimated probability of being alive at 1 year of 30%. Toxicity was acceptable among all arms, although more pronounced in the combination arm. On the basis of the results of the MILES trial, the ASCO recommends single-agent therapy as the treatment of choice for elderly population [84].

The discrepancy between the SICOG [97] and MILES [99] trials could be due to differences regarding patient sample. Interestingly, the SICOG trial reported a very poor median survival for patients treated with vinorelbine monotherapy. Indeed, median survival of 18 weeks reported by SICOG [97, 98] is remarkably lower than the 28 weeks of median survival reported for vinorelbine monotherapy in phase III trials for elderly population [95, 99] and is similar to that reported for BSC in the ELVIS trial [95].

A recently published meta-analysis assessed the efficacy and tolerability of a gemcitabine third-generation agent doublet versus single-agent treatment in elderly NSCLC patients [100]. While significantly higher overall response rate (ORR) was observed [combination versus single agent; odds ratio (OR): 0.65; \( P < 0.001 \)], there was only a trend toward higher survival in favor of combination treatment (OR: 0.78; \( P = 0.169 \)) [100]. Toxicity was not significantly different, except for thrombocytopenia.

single agent versus platinum-based doublet. A docetaxel/cisplatin doublet was compared with docetaxel monotherapy in the context of a randomized phase III trial for elderly NSCLC patients [101]. Patients included were ≥70 years old and were randomized to receive either docetaxel/cisplatin (docetaxel 20 mg/m², cisplatin 25 mg/m², on days 1, 8 and 15) or docetaxel monotherapy (25 mg/m², on the same schedule). The planned sample size was 115 patients per arm, but the study was prematurely closed after randomization of only 63 patients per arm when a planned interim analysis showed a strong indication that the doublet may be beneficial for the subgroup of patients aged 70–74 years. The premature termination of the study on the basis of a subgroup benefit complicates the interpretation of the observed results.

Cisplatin in combination with a third-generation agent offers a small survival benefit as first-line treatment when compared with carboplatin third-generation agent doublets [102]. On the other hand, carboplatin has a more favorable toxicity profile when compared with cisplatin, in terms of nausea, vomiting and renal toxicity [102] and makes platinum-based treatment feasible in elderly patients, who, because of cardiopulmonary

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comorbidities and renal insufficiency, are not candidates for cisplatin. Furthermore, given the unquestionable practical advantage of carboplatin in terms of ease of administration, it could be argued that the small benefit achieved with cisplatin relative to carboplatin does not justify its use in clinical practice. A randomized phase III trial compared single-agent gemcitabine with gemcitabine/carboplatin doublet as first-line treatment of NSCLC patients [103]. A preplanned subgroup analysis of elderly patients (n = 121) indicated that both young and elderly patients showed benefit in OS when treated with the combination regimen. Although this gain was significant only for young patients (aged <70 years) (P = 0.03), the elderly patients also showed a trend for increased OS on the combination arm (P = 0.2) [103]. Elderly patients experienced more hematological toxicity when compared with younger patients [103]. Additionally, a subgroup analysis of a study comparing paclitaxel monotherapy to a paclitaxel/carboplatin doublet indicated that elderly patients derived benefit from the combination regimen (median OS for monotherapy versus doublet: 5.8 versus 8.0 months; P = nonsignificant). It is likely that the lack of statistical significance is related to the small number of patients [104] (Table 3).

Table 3. Retrospective trials of platinum-based chemotherapy comparing treatment outcomes between younger and elderly non-small-cell lung cancer patients

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Treatment</th>
<th>ORR (%)</th>
<th>TTP (mo)</th>
<th>P value</th>
<th>OS (mo)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sederholm et al. [103]</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 years old</td>
<td>213</td>
<td>Carbo/CMB versus GMB</td>
<td>18.6</td>
<td>NR</td>
<td>0.004*</td>
<td>NR</td>
<td>0.20</td>
</tr>
<tr>
<td>270 years old</td>
<td>121</td>
<td></td>
<td>22.1</td>
<td></td>
<td></td>
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<tr>
<td>Lilenbaum et al. [104]</td>
<td></td>
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</tr>
<tr>
<td>&lt;70 years old</td>
<td>406</td>
<td>PCL versus Carbo/PCL</td>
<td>15^5; 28^6</td>
<td>6.8^6; 9.0^6</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>270 years old</td>
<td>155</td>
<td></td>
<td>21^5; 36^6</td>
<td>5.8^6; 8.0^6</td>
<td>NS</td>
<td></td>
<td></td>
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<tr>
<td>Langer et al. [105]</td>
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<tr>
<td>&lt;70 years old</td>
<td>488</td>
<td>CDDP/PCL (135 mg/m^2 or 250 mg/m^2) versus VP/CDDP</td>
<td>21.3</td>
<td>4.37</td>
<td>0.29</td>
<td>9.05</td>
<td>0.29</td>
</tr>
<tr>
<td>270 years old</td>
<td>86</td>
<td></td>
<td>23.3</td>
<td>4.30</td>
<td></td>
<td>8.53</td>
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<tr>
<td>Langer et al. [106]</td>
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<tr>
<td>&lt;70 years old</td>
<td>912</td>
<td>CDDP/PCL versus CDDP/GMB</td>
<td>22.1</td>
<td>3.71</td>
<td>8.15</td>
<td></td>
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</tr>
<tr>
<td>270 years old</td>
<td>227</td>
<td>CDDP/PCL versus CDDP/TXT versus</td>
<td>24.5</td>
<td>3.75</td>
<td></td>
<td>8.25</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Carbo/PCL</td>
<td></td>
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<tr>
<td>Kelly et al. [107]</td>
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<tr>
<td>&lt;70 years old</td>
<td>491</td>
<td>CDDP/VNB or Carbo/PCL</td>
<td>NR</td>
<td>4.2</td>
<td>0.62</td>
<td>8.6</td>
<td>0.06</td>
</tr>
<tr>
<td>270 years old</td>
<td>117</td>
<td></td>
<td>3.9</td>
<td></td>
<td></td>
<td>6.9</td>
<td></td>
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<tr>
<td>Belani and Fossella [108]</td>
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<td></td>
<td></td>
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<tr>
<td>&lt;65 years old</td>
<td>817</td>
<td>CDDP/TXT versus Carbo/TXT versus</td>
<td>11 versus 12.6</td>
<td>9.7 versus 9.0</td>
<td>NS</td>
<td></td>
<td></td>
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<tr>
<td>265 years old</td>
<td>401</td>
<td>CDDP/VNB</td>
<td></td>
<td></td>
<td></td>
<td>10.1 versus 9.9</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>versus CDDP/VNB</td>
<td></td>
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<tr>
<td>Hensing et al. [109]</td>
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<tr>
<td>&lt;70 years old</td>
<td>163</td>
<td>Carbo/PCL for 4 cycles versus</td>
<td>20</td>
<td>3</td>
<td>0.049</td>
<td>7.8</td>
<td>NS</td>
</tr>
<tr>
<td>270 years old</td>
<td>67</td>
<td>until progression</td>
<td>27</td>
<td>4.8</td>
<td></td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Goto et al. [110]</td>
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</tr>
<tr>
<td>&lt;70 years old</td>
<td>497</td>
<td>CDDP/CPT versus Carbo/PCL</td>
<td>26^d</td>
<td>NR</td>
<td>48%^d</td>
<td></td>
<td></td>
</tr>
<tr>
<td>270 years old</td>
<td>105</td>
<td>versus CDDP/GMB versus CDDP/VNB</td>
<td>20^d</td>
<td></td>
<td>48%^d</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>32^d</td>
<td></td>
<td>61%^d</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>50^d</td>
<td></td>
<td>46%^d</td>
<td>(1-year survival)</td>
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</tr>
<tr>
<td>Amari et al. [111]</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 years old</td>
<td>314</td>
<td>Carbo/GMB versus PCL/GMB</td>
<td>37.5</td>
<td>5.3</td>
<td>NS</td>
<td>8.3</td>
<td>NS</td>
</tr>
<tr>
<td>270 years old</td>
<td>746</td>
<td>versus Carbo/PCL</td>
<td>36</td>
<td>4.8</td>
<td></td>
<td>7.9</td>
<td></td>
</tr>
</tbody>
</table>

*In favor of the elderly patients.
^For PCL.
^For Carbo/PCL.
^Data reported for patients ≥70 years old.
ORR, overall response rate; TTP, time to tumor progression; OS, overall survival; NR, not reported; NS, nonsignificant; CDDP, cisplatin; PCL, paclitaxel; VP, etoposide; GMB, gemcitabine; TXT, docetaxel; Carbo, carboplatin; VNB, vinorelbine; CPT, irinotecan.
tumor progression (TTP) [103, 109] and 2-year OS [106] for the elderly population. Regarding severe toxicity (grade ≥3), some studies report a higher incidence in elderly patients [103, 105, 108, 110, 111], while others do not [106, 107, 109]. A large phase III trial supported that docetaxel/platinum doublets offer a survival benefit as first-line treatment when compared with vinorelbine/cisplatin doublet [112]. An age-specific subgroup analysis of 401 elderly (aged ≥65 years) patients indicated that elderly patients treated with platinum-based combination chemotherapy had similar survival rates to younger patients [108]. In the cohort of elderly patients, median OS was 12.6 months in the docetaxel–cisplatin arm and 9.9 months in the vinorelbine–cisplatin arm; 1-year survival was 52% and 41%, respectively, and 2-year survival was 24% and 17%, respectively. Survival results for elderly docetaxel–carboplatin-treated patients were similar to those for elderly vinorelbine–cisplatin-treated patients. Compared with younger patients, elderly patients reported moderately higher incidence of grades 3–4 asthenia, infection, and pulmonary toxic effects across treatment arms, and diarrheea and sensory neurotoxicity for cisplatin-containing arms [108]. Finally, an age-specific subgroup analysis for elderly patients of a phase III trial comparing weekly versus standard schedules of paclitaxel/carboplatin combination reported similar outcome for the two schedules, although weekly administration had a more favorable toxicity profile [113].

It should be emphasized that the above-mentioned data are derived from retrospective analyses, which inherently suffer from selection bias due to inclusion of only those elderly patients considered by their treating physician to be able to tolerate the toxicity of cytotoxic chemotherapy. Consequently, any extrapolation of these results to the general elderly population should be taken with caution.

A recently published Italian study examined the feasibility of cisplatin-based doublets in elderly NSCLC patients [114]. Two doublets were evaluated in 159 elderly (aged ≥70 years) NSCLC patients: cisplatin/gemcitabine and cisplatin/vinorelbine. Both doublets were shown to be feasible and active in elderly. On this basis, it is clear that further, prospective comparative phase III trials of platinum-based doublets versus single agent are needed.

pooled analyses. Recently, Hellenic Oncology Research Group published the results of a pooled analysis of elderly patients with NSCLC treated with front-line docetaxel/gemcitabine [115]. A total of 858 patients participating in six clinical trials were analyzed and 192 (22.4%) patients were ≥70 years old. The ORR was 30.3% and 30.2% for patients aged <70 and ≥70 years, respectively (P = 0.974). The median TTP was 4.1 and 4.5 months (P = 0.948) and median OS was 9.9 and 9.2 months (P = 0.117) for patients aged <70 and ≥70 years, respectively. Multivariate analysis revealed PS (P = 0.0001) and stage (P = 0.0001), but not age, as independent factors with significant impact on the hazard of death. Chemotherapy was well tolerated, but the incidence of grades 3/4 mucositis (P = 0.011) and diarrhea (P = 0.051) was significantly higher in elderly patients.

Another pooled analysis of six clinical trials was reported by the Spanish Lung Cancer Group [116]. Of the 1653 patients included in three clinical trials, 280 (17%) were aged ≥70 years. Median TTP (young versus elderly: 4.4 versus 4.5 months; P = 0.49) and median OS (young versus elderly: 7.6 versus 7.5 months; P = not reported) were almost identical between age groups. Similarly, 1- and 2-year survival rates were 35% and 14% and 42% and 16% for the young and elderly patient groups, respectively. No difference was observed in the median number of cycles administered, while elderly patients experienced more grades 3/4 neutropenia than younger patients did (young versus elderly: 20% versus 26%; P = 0.03).

octogenarians. In general, few data exist regarding the outcome of chemotherapy in NSCLC patients aged ≥80 years, a rapidly expanding, potentially vulnerable population cohort. A retrospective chart review of 111 octogenarians diagnosed with any stage of NSCLC shows that the vast majority of them received therapy, but only one-third were treated with stage-specific guideline-recommended therapy [106, 117, 118]. Patients ≥80 years of age fared worse than patients aged 70–79 years in terms of OS, although it should be noted that only a very small number of patients aged ≥80 years were enrolled (nine patients in the ECOG trial [106] and 26 and 23 in the Southwest Oncology Group 0027 and LUN 6 trials [118], respectively). In a retrospective review of 46 octogenarians reported by the MD Anderson Cancer Center, elderly and younger patients had similar response rate (41% versus 47%), median PFS (5.55 versus 3.91 months; P = 0.216) and median OS (10.7 versus 9.8 months; P = 0.43), without significant increase in toxicity [119]. The lack of data on octogenarians remains troublesome. Based on retrospective analyses, clinicians should exercise caution when applying the existing data for patients aged 70–79 years to those aged ≥80 years [120]. Clearly, more data are needed on appropriate therapy recommendations for this patient population and more studies need to be conducted. This group is a particularly attractive target for studies using molecular targeted and other potentially less toxic oral single agents.

targeted agents. A recently published randomized phase III trial has proved that the addition of bevacizumab to standard paclitaxel/carboplatin doublet as first-line treatment of nonsquamous NSCLC patients results in significant prolongation of PFS and OS [121]. Of the 878 patients who entered the original trial, 224 (26%) were aged ≥70 years. A subgroup analysis for these patients was reported [122]. An age by treatment interaction term was added to a Cox model and showed that treatment effects were not different for young and elderly patients (P = 0.34). Furthermore, another Cox model demonstrated that age was not a negative prognostic factor for survival. Nevertheless, the addition of bevacizumab to paclitaxel/carboplatin doublet in the elderly population did not result in a significant prolongation of median OS, and there was only a trend toward higher PFS in favor of bevacizumab arm. Nevertheless, it should be noted that the subgroup analysis did not have power to detect a survival difference. An important observation is that the addition of bevacizumab resulted in significantly more grade ≥3 toxic effects in elderly patients compared with the paclitaxel/carboplatin doublet. Seven
treatment-related deaths were observed among elderly patients treated with the paclitaxel/carboplatin/bevacizumab combination. Additionally, elderly patients treated with the three drug combination suffered more grade 3 toxic effects compared with their younger counterparts [122]. Further evaluation of bevacizumab combined with different chemotherapy regimens (single agent or platinum-based doublets with modified doses and schedules) are warranted [123].

A randomized phase II trial compared gefitinib with vinorelbine (30 mg/m² on days 1 and 8 of a 21-day cycle) in chemotherapy-naïve elderly (≥70 years of age) patients [124]. A total of 196 patients were enrolled (gefitinib, n = 97; vinorelbine, n = 99). There were no differences between the gefitinib and the vinorelbine arms in terms of response rate (3.1% versus 5.1%), PFS (median PFS: 2.7 versus 2.9 months) and OS (median OS: 5.9 versus 8.0 months). Overall QoL improvement rates, as assessed by the total Functional Assessment of Cancer Therapy-Lung scores, were higher with gefitinib than with vinorelbine (24.3% versus 10.9%). There were fewer treatment-related grades 3–5 adverse events with gefitinib (12.8%) than with vinorelbine (41.7%). An unexpected observation was that epidermal growth factor receptor (EGFR) FISH-positive patients benefited more from vinorelbine than from gefitinib [124].

Jackman et al. have evaluated erlotinib as first-line treatment in 80 elderly (≥70 years of age) NSCLC patients in the context of a phase II trial [125]. Eight patients experienced partial responses (10%) and 33 (41%) had stable disease. The median TTP was 3.5 months and median OS was 10.9 months. The 1- and 2-year survival rates were 46% and 19%, respectively. The most common toxic effects were acneiform rash (79%) and diarrhea (69%). Four patients developed interstitial lung disease of grade 3 or higher, with one treatment-related death.

Gridelli et al. evaluated in a randomized phase II trial the optimal way of combining gemcitabine and cetuximab (either concurrently or sequential, gemcitabine followed by cetuximab) in elderly NSCLC patients [126]. Sequential approach was not recommended for further study because of low compliance, while the concurrent approach was not proposed for further development due to inconsistency of survival outcomes.

recommendation. For the elderly population, the available data indicate that third-generation single agent should be used as first-line NSCLC treatment. Published data support the use of vinorelbine, gemcitabine or docetaxel monotherapy. Docetaxel produces higher PFS when compared with vinorelbine but without a difference in OS. Very limited data are published regarding octogenarians, and thus, no specific recommendations can be made for this particular age group.

Given that the addition of bevacizumab to standard cytotoxic chemotherapy in elderly population results in significant toxicity, while it is not clear whether it offers a survival benefit or not, prospective studies to assess the therapeutic index of the combination of chemotherapy with a targeted agent in the elderly are needed, before definitive recommendations regarding their use can be made. Erlotinib monotherapy is active and relatively well tolerated in elderly patients with advanced NSCLC. Nevertheless, because these data are based on phase II trials, further investigation in the context of randomized phase III trials of selected patients based on validated molecular markers (e.g. EGFR mutations) are needed.

second-line treatment

Three agents have been approved for the second-line treatment of NSCLC: docetaxel, pemetrexed and erlotinib [127–130]. A recent publication reported the results of an age-specific subgroup analysis of a randomized phase III trial comparing pemetrexed with docetaxel in pretreated patients with NSCLC [131]. The original trial randomized 571 previously treated NSCLC patients [129]. Eighty-six of those (15%) were ≥70 years old. Objective response rates, median PFS and median OS were not significantly different between younger and elderly patients, irrespective of the treatment arm. Elderly patients had a median OS of 9.5 and 7.7 months in the pemetrexed and docetaxel arms, respectively, while for younger patients, the corresponding OS were 7.8 and 8.0 months for pemetrexed and docetaxel arms, respectively. Furthermore, no significant difference between younger and elderly patients was reported regarding toxicity. The authors concluded that second-line cytotoxic treatment is feasible for elderly patients, with pemetrexed producing a more tolerable toxicity profile compared with docetaxel. Nevertheless, as this is a retrospective analysis, it is likely to suffer from selection bias.

targeted agents. The National Cancer Institute of Canada—Clinical Trials Group conducted a phase III trial (BR.21 study) that randomly assigned patients who had experienced failure with first- or second-line chemotherapy to erlotinib or placebo in a 2 : 1 ratio. Treatment with erlotinib resulted in a significant survival benefit over placebo [130]. This study included 163 (22% of the original cohort; 112 on erlotinib, 51 on placebo) patients ≥70 years old [132]. No significant difference was observed between young and elderly patients in terms of response rate, PFS and OS (erlotinib arm: 6.4 versus 7.6 months for young and elderly patients, respectively; P = 0.85; placebo arm: 4.7 versus 5.0 months for young and elderly patients, respectively; P = 0.22). Similarly, treatment effect did not differ significantly between young and elderly patients, with the latter deriving the same benefit from erlotinib treatment as their younger counterparts. Although fatal treatment-related adverse events were unusual, elderly patients experienced significantly more grade 3 toxic effects (35% versus 18% for elderly and young patients, respectively; P < 0.001). Thus, erlotinib is a reasonable treatment option for elderly patients with advanced NSCLC in the salvage setting. The presence of EGFR gene mutations in the tumor has emerged as a promising predictor of efficacy with EGFR tyrosine kinase inhibitors [133]. Validation of these markers in prospective studies will further optimize the use of erlotinib in all patients including the elderly subgroup.

recommendation. There is lack of prospective data regarding the role of second-line treatment in elderly NSCLC population. On the basis of retrospective data, age alone should not prevent the administration of second-line therapy and pemetrexed or erlotinib could be considered as second-line treatment of elderly NSCLC patients. A thorough evaluation of the patient should be done on the basis of life expectancy, expected benefit, comorbidities and patient’s preferences.
As a consequence of increasing life expectancy, lung cancer will continue to evolve as a health problem in the elderly population. Nearly 40% of all new lung cancer cases diagnosed continue to evolve as a health problem in the elderly as a consequence of increasing life expectancy, lung cancer will evolve as a health problem in the elderly population. As a result of this increased life expectancy, lung cancer will continue to be a significant health problem in the elderly population. In addition, the incidence and prevalence of lung cancer in the elderly population have increased significantly in recent years. Aging is associated with several physiologic changes in organ function that could alter drug pharmacokinetics and have an impact on the tolerability of cytotoxic chemotherapy. Renal function as indicated by the glomerular filtration rate is reduced with age [135] and could have an impact on pharmacokinetics and pharmacodynamics of various chemotherapeutic agents such as cisplatin or pemetrexed [120, 136]. Similarly, impaired liver metabolism and hypoalbuminemia are frequently observed in elderly patients [135] and could have an impact on vinorelbine and taxane metabolism and pharmacokinetics [120]. Furthermore, in the elderly, the amount of body fat is increased and the intracellular water is decreased, having as a sequence a reduced volume of distribution and higher peak concentration of hydrophilic drugs, while lipophilic drugs will have an increased distribution and prolonged half-life [137]. Bone marrow reserves also diminish with increasing age and myelotoxicity can be substantially increased [135]. Changes with age within the gastrointestinal system can result in decreased gastrointestinal motility, reduced splanchic blood flow and secretion of digestive enzymes and mucosal atrophy and thus increasing the incidence of mucositis [138]. Furthermore, elderly patients who receive taxane-based therapy have a great risk of developing peripheral neuropathy [139]. All these factors should be taken into account when deciding whether or not to treat an elderly cancer patient, especially when selecting the proper treatment.

Moreover, aging is associated with a significant prevalence of comorbid diseases. A thorough assessment of comorbidities in cancer patients is required because it will determine the patients’ life expectancy (i.e., more immediate medical problem could have more impact on the patient’s life before the cancer itself becomes life threatening). Comorbidities can have a significant impact on patient PS and may have an impact on patient ability to tolerate treatment or may be a contraindication for cancer treatment (e.g., trastuzumab in patients with congestive heart failure). Furthermore, coexisting medical problems also lead to significant use of medication and polypharmacy has been reported as a significant factor, which contributes to increased chemotherapy toxicity [140, 141].

Additional important issues regarding treatment of elderly cancer patients are the presence of geriatric syndromes (dementia, delirium, depression, falls, neglect and abuse, spontaneous bone fractures and fall to thrive), the level of social support provided and the nutritional status of the elderly patient. Presence of dementia has been reported as a negative prognostic factor for survival [142] and absence of adequate social support has been reported as a predictor of mortality in the elderly population [143]. Poor nutritional status results in diminished 1-year survival among the elderly people [144].

When evaluating different treatment options for elderly patients with NSCLC, it is very important to select only those patients suitable for a given treatment. Such suitability should not be defined solely on the basis of chronological age. Aging is a highly individualized process and all the changes that occur cannot be predicted on the basis of chronological age alone. A more thorough method, such as the comprehensive geriatric assessment (CGA), should be used when evaluating elderly cancer patients. The CGA estimates a patient’s functional status, the presence of comorbidities, mental status and emotional conditions, nutritional status, polypharmacy and the presence or absence of geriatric syndromes [145]. The nature of CGA and its ability to detect health problems in elderly patients were reviewed by Maas et al. [146]. Beyond chronological age [146] or PS [147], this assessment also allows the identification of potentially treatable problems (such as depression or malnutrition) that may otherwise decrease tolerability and increase toxicity and consequently compromise treatment outcome. Wymenga et al. have demonstrated that CGA can predict toxicity in elderly NSCLC patients receiving combination chemotherapy and thus might allow patient selection for such treatment [148]. The International Society of Geriatric Oncology recommends using CGA in elderly cancer patients, although the best form of CGA for cancer patients remains to be defined [149]. Nevertheless, on the other hand, CGA has never been prospectively validated as a prognostic and predictive factor for treatment-related toxicity and outcome. Additionally, the full CGA is a time-consuming procedure and often impractical in everyday clinical practice. Some more short adaptation of CGA would probably be more preferable and practical to adapt to every day’s clinical practice [150].

Conclusions: NSCLC represents a significant health problem in the elderly population, and specific considerations regarding treatment of this population have been presented in this review. Functional impairment and comorbidity and not chronological age effect treatment tolerance and effectiveness in elderly patients with NSCLC. Nevertheless, with the exception of advanced/metastatic NSCLC, the consensus and suggestions for management are based on retrospective data or subanalyses from general population studies, which have included predominantly younger patients or the fittest older patients. These are likely to be biased in favor of treatment, as only elderly patients considered “healthy enough” would have entered those studies. There is an acute need for prospective elderly-specific NSCLC trials.

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