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Review

Treatment of elderly patients or patients who are performance status 2 (PS2) with advanced Non-Small Cell Lung Cancer without epidermal growth factor receptor (*EGFR*) mutations and anaplastic lymphoma kinase (*ALK*) translocations – Still a daily challenge

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Abstract Cytotoxic chemotherapy remains the core treatment strategy for patients with advanced non-small cell lung cancer (NSCLC) with tumours that do not have actionable molecular alterations, such as epidermal growth factor receptor (*EGFR*)-sensitising mutations, anaplastic lymphoma kinase (*ALK*) translocations or *ROS1* translocations. Age and performance status (PS) are two pivotal factors to guide treatment decisions regarding the use of chemotherapy in lung cancer patients. Lung cancer is predominantly a disease of the elderly, with more than two-thirds of patients aged ≥65 years, the current definition of 'elderly'. The prevalence of poor PS, as estimated by patients themselves, can be as high as 50%. Both the elderly and PS2 patients are underrepresented in clinical trials. Therefore, optimising treatment strategy for the subgroup of elderly or PS2 patients with advanced NSCLC remains challenging as a result of a paucity of clinical trial data. The current review focusses on the elderly or PS2 patients without actionable oncogenic drivers and attempts to summarise current available data on recent treatments trials including angiogenesis inhibitors and immune-checkpoint inhibitors.

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1. Introduction

Treatment strategy for patients with advanced non-small cell lung cancer (NSCLC), the dominant subtype of lung cancer, has changed over the past decade [1]. In the new era of precision medicine, molecularly targeted therapy has profoundly changed the outcomes for patients with actionable molecular abnormalities, including epidermal growth factor receptor (*EGFR*) treatment-sensitising mutations [2–8], anaplastic lymphoma kinase (*ALK*) translocations [9,10], and *ROS1* translocations – even in the elderly patients and patients with a performance status (PS) of 2 [11–13]. Compared with conventional chemotherapy, targeted therapies manifest modest toxicities but superior clinical efficacy [1]. However, for the patients without oncogenic drivers, chemotherapy is still the standard of care in routine clinical practice (Tables 1–4).

Lung cancer is predominantly a disease of the elderly, with more than two-thirds of patients aged ≥65 years (the definition of elderly) [14,15]. Age itself **IS NOT** a prognostic factor in most studies [16–19]. However, age does predict for more toxicities and because of certain comorbidities, there are drug and dose restrictions e.g. with the use of cisplatin or an anthracycline. Increasing age is associated with a greater burden of comorbidities [20]. Age **IS NOT** a predictive factor – most treatments that can be given to the elderly are equally active according to the trials with sufficient power to support this. Therefore, elderly patients are at risk of undertreatment and at risk of overtreatment toxicities in routine clinical practice [21].

Patients with an Eastern Cooperative Oncology Group (ECOG) Performance Status of 2 account for 30–40% of the patients with NSCLC [22,23]. PS **IS** a prognostic factor in most studies and also predicts for more toxicities. PS **IS** also a predictive factor for response – most treatments are less active in PS2 patients (response rates, survival etc.) than in PS1 or 0 patients. PS is determined by both cancer-related symptoms and comorbidities that are unrelated to cancer. However, no studies have shown that PS2 patients have more comorbidities that PS1 patients [24].

Currently, age and PS are the two key factors to guide treatment decisions regarding the use of chemotherapy [25–27]. Age is a discrete variable but PS can be difficult to assess reproducibly. The use of other prognostic indexes e.g. the Glasgow prognostic scale – which uses only C reactive protein (CRP) and serum albumin, has not been evaluated specifically in the elderly or PS2 patients.

Clinical trials in both the elderly and PS2 patients should be done with prophylactic growth factors (such as granulocyte colony-stimulating factors (G-CSF)), haematinics (such as iron, folic acid, vitamin B12, erythropoietin etc.) and antibiotics [28–31] to avert predictable and potentially avoidable toxicities. The current review focusses on elderly or PS2 patients without oncogenic drivers and summarises current evidence for the treatment of these subgroups with advanced NSCLC.

2. Treatment of elderly patients with advanced NSCLC

2.1. Combination chemotherapy

According to American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) guidelines [32,33], for all patients (regardless of age) without *EGFR*-sensitising mutations or *ALK* gene translocations and PS 0 to 1, two drugs combination is recommended. Platinum-based doublets are preferred over non-platinum doublets. A variety of platinum-based combinations have been approved, including docetaxel/gemcitabine/paclitaxel/vinorelbine/nab-paclitaxel/ pemetrexed plus cisplatin/carboplatin. Based on histology, pemetrexed-based combination is only approved for patients with non-squamous NSCLC.

The first trials in the elderly used single agent chemotherapy drugs. However the current guidelines are based on the most recent trials of combinations. The Intergroupe Francophone de Cancerologie Thoracique (IFCT)-0501 trial demonstrated a survival benefit in favour of a platinum-based doublet compared to a single-agent chemotherapy in elderly patients with advanced NSCLC [34]. In IFCT-0501, 451 patients aged ≥70 years were randomly assigned to receive weekly paclitaxel (90 mg/m^2) plus carboplatin or monotherapy (gemcitabine or vinorelbine). The combination regimen resulted in a clear benefit in terms of overall survival (OS) (10.3 versus 6.2 months; hazard ratio [HR], 0.64; 95% confidence interval [CI], 0.52–0.78; $p < 0.0001$), progression-free survival (PFS) (6.0 versus 2.8 months; HR, 0·51; 95%CI, 0·42–0·62; $p < 0·0001$), and 1-year survival rate (44.5% versus 25.4%; $p < 0·0001$). The combination regimen was associated with significantly higher incidence of grade ≥3 neutropenia, febrile neutropenia (FN), thrombocytopaenia, anaemia and sensory neuropathy, but quality of life (QOL) was not adversely affected [34]. In a north Japan lung cancer group trial [35], the combination regimen (weekly paclitaxel [70 mg/m^2]) plus carboplatin) also significantly improved PFS (6.6 versus 3.5 months) and objective response rate (ORR) (54% versus 24%) compared with single-agent docetaxel (60 mg/m^2). In general, in all age groups weekly paclitaxel plus carboplatin is not a standard regimen in NSCLC treatment currently due to the equivalent results when it was compared to standard 3-weekly paclitaxel and carboplatin [36]. However, in that study there was less grade 3 and 4 neuropathy and arthralgia with the weekly paclitaxel combination, which is why it is more acceptable for an elderly population. Phase III studies with a docetaxel platinum combination also failed to