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Review

Lung cancer management: challenges in elderly patients

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Elderly patients represent the majority of lung cancer cases, but they are often under-represented in clinical cancer treatment trials or excluded from studies because of comorbidities. Due to lack of data, treatment options for this population must be carefully evaluated and preliminary assessment should aim to stratify patients into different risk subgroups. In early NSCLC stages, surgery remains the best therapeutic option in low-moderate risk patients. Conversely, in patients unfit for surgery or in advanced stages, chemotherapy and radiotherapy should be considered as they may offer benefits in terms of clinical outcomes. Recent developments in targeting driver genes mutations as well as immune checkpoints have opened novel horizon in lung cancer management and systematic investigation in elderly population is required. In this review, we examined the more recent results of the literature about the therapeutic scenario in limited and advanced lung cancer stages in elderly and very elderly population.

Key words: Lung cancer, Surgery, Chemotherapy, Radiotherapy, Immunotherapy, Elderly

INTRODUCTION

Lung cancer (LC) has long been considered one of the most prevalent cancers in the world. Since the 1930s, both incidence and mortality rates of LC have been rising steadily [1] and in 2012 resulted in more than 1.6 million deaths worldwide [2]. LC incidence increases with age: in the United States 68% of the patients are diagnosed after 65 years of age [3] and in UK the peak incidence of LC is between 75 and 80 years of age [4].

Tobacco smoking and air pollution exposure remains the major risk factors for lung cancer development [5-9]. Although elderly patients represent the majority of lung cancer cases, they are under-represented in clinical cancer treatment trials, with only 25% of enrolled patients over 65 years old [10]. In fact, subjects aged more than 70 years have been excluded from almost all clinical trials of cancer treatment-especially phase I/II studies and pharmacokinetic evaluations of new drugs [11]. In addition, the definition of "elderly" in oncology is still under debate. Whereas in Europe and in the US the threshold of 70 years is accepted to define a patient "elderly" [12], some authors define the geriatric oncology group as patients in which clinical status begins to interfere with oncologic decision making [13 14]. The elderly represents a complex patient group with increasing comorbidity, shrinking physiological reserve, limited expectations for long-term benefit of chemotherapy [15-18].

The prevalence of comorbidities among LC patients is significantly higher in patients aged > 70 years, coupled with a proportionate increase in the number of co-morbidities per patient [19-23]. On the other hand, age by itself should not be a limit to the diagnosis or therapy. Older subjects obtain lower histological confirmation rates and less accurate staging than younger patients [24].

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Ayyappan et al. found that one-third of the very elderly, defined as patients over 80 years old, were diagnosed with LC without tissue confirmation [25].
Brown et al. showed that the use of surgery and chemotherapy in patients with Non-Small Cell Lung Cancer(NSCLC) was 18 and 21%, respectively, of patients aged < 65 years compared with 2.1 and 0% for patients aged > 75 years [4]. This review examines the main results from the literature regarding therapy in limited and advanced LC stages in elderly and very elderly population.

WHICH ROLE FOR SURGERY IN EARLY STAGES

Elderly patients affected by NSCLC are a heterogeneous group and they should be accepted for lung surgery on the basis of cardiac, pulmonary, geriatric and cognitive evaluation. The American Heart Association (AHA) and the American College of Cardiology (ACC) provided guidelines for preoperative cardiovascular assessment for non-cardiac surgery at all ages [26] considering six independent predictors of complications [27]. ECG and echocardiography should always be performed, whilst other non-invasive testing (e.g. lower limbs vein ultrasonography) should be performed before surgery in patients with history of angina or claudication. Pulmonary functional and comorbidities evaluation is mandatory at any age before considering patient for lung resection [16 28-31]. ERS algorithm is recommended for physical evaluation in patients undergoing lung resection. The predicted post-operative FEV_1 (ppo-FEV_1) is the most commonly used test for including or excluding patients or to consider further tests [32]. A value of ppo-FEV_1 < 40% is currently used to distinguish between normal risk and higher risk lung resection patients [33]. In patient hemodynamically stable, a stair climbing test (SCT) is recommended. In case of SCT result below 22 m, exertional test should be performed in addition to VO2max estimation to stratify patients in 3 groups: low risk (VO2max > 20 mL/kg/min) intermediate risk (VO2max 10-20 mL/kg/min) and high risk (VO2max < 10 mL/kg/min) [34]. Preoperative rehabilitation can be offered in patients with reduced functional reserve and may improve exertional parameters [35 36]. Geriatric evaluation is suggested from the International Society of Geriatric Oncology (ISGO) which proposed the “Preoperative Assessment of Cancer in Elderly” (PACE) to assess surgical risk in this specific population, though the performance status (PS) as measured by Karnofsky and ECOG scales remains the most appropriate for patients with lung cancer undergoing surgery [37]. However, the impact of surgery on functional decline/recovery and permanent loss of independence remains not straightforward to define. In addition to standard cardio-respiratory evaluation, nutritional assessment should be included in the routine preoperative selection as malnutrition has been reported as being a significant additional risk factor for early death. Thus, in malnourished patients, nutritional support before and after operation and careful post discharge care might be beneficial [38]. In addition, educational strategy seems to be effective in elderly patients in reducing the length of stay in elderly frail subjects [39].
The best surgical approach in elderly patients is still object to debate. Lobectomy with radical lymphadenectomy remains the treatment of choice in Stage I and II NSCLC patients. In selected cases, Zuin et al. reported that more extensive resections such as bilobectomy and/or pneumonectomy could be still justified in patients > 75 year-old as short- and long-term outcomes can be acceptable and comparable with those of younger patients [40]. However, pneumonectomy should be considered extremely carefully as it is associated with significant morbidity and mortality, and more limited resections such as lobectomy associated with broncho-vascular reconstructions, if technically feasible, could be a valid alternative [41 42].
In elderly patients who were unfit for anatomical resections due to poor respiratory condition, several studies showed sub-lobar resection presented similar survival to more extended resections. Razi et al. in a retrospective study including 1640 patients aged > 75 years with stage IA NSCLC found that in high risk patients sub-lobar resection was not inferior to lobectomy [43]. Fiorelli et al. [44] in a multicenter study including 239 patients (aged 75 year-old) compared lobectomies (n = 149) versus sub-lobar resection (n = 90). The authors found no differences in the recurrence rates following lobar versus sub-lobar resections (19 *versus* 23%, respectively; p = 0.5) on the overall survival (p = 0.1), cancer-specific survival (p = 0.3) or disease-free survival (p = 0.1). After adjusting for 1:1 propensity score matching and a matched pair analysis, the results remained unchanged. Tumor size > 2 cm and pN2 disease were independent negative prognostic factors in unmatched (p = 0.01 and p = 0.0003, respectively) and matched (p = 0.02 and p = 0.005, respectively) analyses. De Giacomo et al. confirmed these results and found no significant difference in terms of recurrence between patients undergoing lobectomy compared to those undergoing sub-lobar resections [45]. In theory, the thoracoscopic approach could be a valid alternative to traditional thoracotomy in elderly patients in order to reduce the surgical trauma and thus post-operative morbidity and mortality [46-50].

RADIOTHERAPY AND NON-SURGICAL APPROACH IN LIMITED DISEASE

Radiotherapy (RT) plays a major role in the curative and palliative treatment of patients with locally advanced NSCLC, particularly since most patients are not suitable for surgery or chemotherapy due to the disease extension, poor PS, advanced age and multiple comorbidities.

RT is commonly used with curative intent in elderly patients with stage I-II NSCLC [51]. This is supported by retrospective case series of elderly patients receiving radical external beam radiotherapy (EBRT) alone for NSCLC with a median survival of up to 37 months for stage I–II disease and 8 months for stage III disease [52-54]. In addition, a large retrospective study by Pignon et al. showed no difference in terms of OS among 1208 patients treated with EBRT between patients ≥ 70 years and < 70 years (p = 0.82) [55]. In patients over 80 years old, there is limited data about the role of radical RT currently available. In a retrospective study by Zachariah et al. on 21 octogenarians treated with RT with curative intent a therapeutic response rate of 77% and completion without interruption in 95% of patients has been reported [56]. A more recent RT technique, called SBRT (Stereotactic body radiotherapy), accurately delivers hypofractionated doses to a precise target using tight margins around the primary tumour. Phase II studies of SBRT for stage I–II NSCLC showed good results in terms of local control and toxicity [57-60]. Hiroshi et al. showed that SBRT was well tolerated with local control rates comparable to surgery [61]. A potential limitation of SBRT in the elderly is the duration of each fraction which can typically last 30 min [62]. Volumetric intensity-modulated arc therapy is currently being used to considerably reduce the duration of each fraction with no difference in terms of quality of treatment plan and comparable healing power [63]. However, for patients with medically inoperable or technically unresectable stage II-III NSCLC combined cytotoxic chemotherapy and RT (CTRT) is established as the standard treatment. Multiple randomized studies and meta-analyses demonstrated that concurrent CT-RT results in improved survival compared with sequential CT-RT or RT alone [64-67].

RT is also used in older patients with Small Cell Lung Cancer (SCLC). In this group of patient RT plays an important role in the management of both limited stage-SCLC (LD-SCLC) and extensive stage-SCLC (EDSCLC) [68]. It is well recognised that the standard of care for patients with higher PS LD-SCLC is early concurrent CTRT with cisplatin (CIS) and etoposide (EP) followed by prophylactic cranial irradiation (PCI) [69]. However, elderly patients are less likely to receive this treatment regimen compared to the younger counterparts [70]. A large international multicentre phase III randomized superiority controlled trial called CONVERT, compared twice daily RT (45 Gy, 1.5 Gy per fraction, 3 weeks) with a dose-escalated once-daily regimen (66 Gy, 2 Gy per fraction, 6.5 weeks) concurrently with Cisplatin/Etoposide (CIS/EP) chemotherapy. The study involved 547 patients affected by SCLC, 15% of them were ≥ 70 years old. Survival outcomes did not differ between twice-daily and once-daily concurrent CTRT in patients with LD-SCLC, and toxicity was similar and lower than expected with both regimens. Since the trial was designed to show superiority of once-daily RT and was not powered to show equivalence, the implication is that twice-daily RT should continue to be considered the standard of care in this setting [71]. Quality of life (QOL), symptom control and toxicity of treatment are of major importance when considering the efficacy of palliative treatments. Elderly people consider mobility and personal care as being the most important factors for QOL. In a prospective study about palliative RT in LC (NSCLC and SCLC), the median survival in the elderly group was reported 6.1 months compared to 4.5 months in the younger group. Symptom palliation rates following RT were similar for the elderly and younger patients. Interestingly, RT toxicity was similar in the younger and elderly groups with 22% of patients experiencing acute dysphagia [72]. Another study by Turner et al. evaluated psychological distress before and after RT using the Hospital Anxiety and Depression Score (HADS) showing no difference between age groups and any improvement after RT [73]. Endobronchial treatment including airway recanalization has been investigated in very recent studies and may guarantee a wider therapeutic choice also in elderly NSCLC patients [74 75].

EFFICACY AND LIMITATIONS OF CHEMOTHERAPY IN ADVANCED DISEASE

The under-representation of elderly patients, in randomized controlled trials (RCTs), results in lack of reliable information about treatment effectiveness and safety for patients in this age group even in advanced disease. As a consequence, the most appropriate regimens for these patients are still controversial, and the role of single-agent or combination therapy is unclear. Firstly, in a multicenter randomized trial, monotherapy with Vinorelbine (VNR) showed improved survival in elderly patients with advanced NSCLC and possibly overall QOL compared to supportive care alone [76]. Furthermore, the results of two phase III trials, namely, the Elderly Lung Cancer Vinorelbine Italian Study (ELCVIS)

and the Multicenter Italian Lung Cancer in the Elderly Study (MILES), documented that the therapeutic benefits of a third-generation anticancer drug alone, such as VNR and gemcitabine (GEM), were superior to best supportive care alone. In the phase III WJTOG9904 trial conducted in Japan, although no significant difference in outcomes was obtained, docetaxel (DTX) alone extended OS and progression-free survival (PFS) compared to VNR alone. Therefore, DTX has been recommended in Japan's guidelines for treatment of lung cancer in the elderly [77].

However, the application of combined therapy with a platinum agent is controversial [78-80]. An epidemiological analysis of US patients treated in clinical practice has shown that the benefit of platinum-based doublet regimens is greater than single-agent chemotherapy but in this study the assignment was not randomized and the results are exacerbated by bias [81]. In 2015 a Cochrane Database systematic review of RCTs in this group of patients assessed the effectiveness and safety of non-platinum single-agent therapy versus non-platinum combination therapy, or non-platinum therapy versus platinum combination therapy in patients over 70 years of age with advanced NSCLC. This study showed that in the elderly patients who do not have significant comorbidities, increased survival with platinum combination therapy needs to be balanced against higher risk of major adverse events when compared with non-platinum therapy [82].

The IFCT-0501 trial is a multicentre, open-label, phase 3, randomised trial which involved patients aged 70-89 years with locally advanced or metastatic NSCLC and WHO PS scores of 0-2. In this trial, the patients received either four cycles (3 weeks on treatment, 1 week off treatment) of carboplatin (CBDCA) (on day 1) plus paclitaxel (PCX) (on days 1, 8, and 15) or five cycles (2 weeks on treatment, 1 week off treatment) of VNR or GEM monotherapy. The primary endpoint was OS, and analysis was done by intention to treat. Toxic effects were more frequent in the doublet chemotherapy group than in the monotherapy group (most frequent, decreased neutrophil count (108 [48.4%] *vs* 28 [12.4%]; asthenia 23 [10.3%] *vs* 13 [5.8%]). Despite increased toxic effects, platinum-based doublet chemotherapy was associated with survival benefits compared with VNR or GEM monotherapy in elderly patients with NSCLC [83]. In 2017 American Society of Clinical Oncology (ASCO) convention two phase 3 studies, MILES-3 and MILES 4, were presented. These studies were conducted in advanced NSCLC patients, > 70 years, ECOG PS 0-1. In MILES-3 patients, independently of histology, were randomly assigned 1:1 to CIS/GEM (Cis 60 mg/m^2 d1, Gem 1000 mg/m^2 dd1,8) or GEM(1200 mg/m^2 dd1,8). In MILES-4 patients with non-squamous histology were randomly assigned 1:1:1:1 to CG, G, CIS/PEM (Cis 60 mg/m^2 d1, Pem 500 mg/m^2 d1) or PEM (Pem 500 mg/m^2 d1). Six cycles were planned. The two trials were closed prematurely because of slow accrual but a joint analysis allowed final analysis to be properly performed, according to IDMC advice. Analysis was based on intention-to treat and adjusted by possible confounding factors. Results: From Mar 2011 to Aug 2016, 531 patients (MILES-3: 299, MILES-4: 232) were assigned to CIS-doublet (n = 263) or single-agent chemotherapy (n = 268). Median age was 75, 79% were male, 70% had non-squamous histology. Median number of cycles was 4 and 3 with and without CIS, respectively. With a median follow-up of 2 years, 384 deaths and 448 PFS events were reported. With and without CIS, median OS was 9.6 *vs* 7.5 months (HR 0.86, 95% CI: 0.70-1.04, p = 0.14); median PFS was 4.6 *vs* 3.0 months (HR 0.76, 95% CI: 0.63-0.92, p = 0.005); response rate was 15.5% *vs* 8.5% (p = 0.02). Significantly more severe hematologic toxicity and fatigue were reported with CIS. Although improving PFS and response rate, addition of CIS to single-agent chemotherapy does not significantly prolong OS of elderly patients with advanced NSCLC. QOL data will be reported separately. Partially supported by AIFA (grant FARM8KAJZK) and Eli Lilly [84]. The Alliance Study A151622 analysed three first-line NSCLC trials: CALGB 9730, CALGB 30203, and CALGB 30801, which tested CBDCA and PCX; CBDCA and GEM; and CBDCA with either PEM or GEM, respectively. OS was the primary endpoint. Secondary endpoints were grade 3–5 adverse events, chemotherapy cycles completed, and whether toxicity prompted chemotherapy discontinuation. 730 patients were included; 337 (46%) were 65+ years of age. No statistically significant difference in survival was observed for older (≥ 65) versus younger patients. A trend emerged with increased odds of a grade 3-5 adverse event for patients ≥ 65 years *versus* < 65 years. The proportion of completed chemotherapy cycles were marginally lower in older patients for those ≥ 65 years *versus* < 65 years, but no statistically significant difference occurred in the rate of chemotherapy discontinuation for patients ≥ 65 years versus < 65 years. These findings support CBDCA doublet-based chemotherapy in select older patients with advanced NSCLC [85]. The PARAMOUNT Phase III trial showed that maintenance PEM after PEM plus CIS induction was well tolerated and effective for patients with advanced non-squamous NSCLC. Approximately 17% of patients receiving maintenance therapy in this study were 70 years of age or older. Continuation maintenance PEM had comparable survival and toxicity profiles in the elderly and non-elderly subgroups.

However, grade 3/4 anemia and neutropenia were numerically higher for elderly patients [86].

The presence of comorbidities is thought to play a significant role in the decision to treat or not treat a given patient. A retrospective study suggested that lung cancer patients may derive a survival benefit from therapies, regardless of the presence of comorbidities, although the degree of benefit seems to decrease with higher Klabunde Comorbidity Index (KCI) scores [87]. Patterns of treatment and survival are largely unknown for older patients with stage III NSCLC in daily clinical practice. An analysis of all patients ≥ 65 years with stage III NSCLC (2009-2013) included in the Netherlands Cancer Registry (NCR) showed that the CTRT was more often applied among patients aged 65-74 years compared to those aged ≥ 75. While survival was worse for patients aged ≥ 75 years, differences between age groups largely disappeared after stratification for treatment.

Less data are currently available about SCLC treatment in the older patient. In patients with limited-stage (LS)-SCLC, the current standard of care for patients eligible for LS-SCLC is thoracic radiotherapy delivered concurrently with double platinum chemotherapy followed by prophylactic cranial irradiation (PCI) in patients without progressive disease [88]. Corso et al. conducted retrospective analysis on available data (2003-2011). This is the first study examining the results of elderly patients (aged 70 years and older) with LS-SCLC after chemoradiotherapy showed a survival benefit of chemoradiotherapy compared to chemotherapy alone (OS 15.6 months versus 9.3 months, respectively, $p < 0.001$) [89].

More recently, Christodoulou et al. have compared the results of patients 70 years of age or older versus younger patients within the Concurrent Once-daily Versus twice-daily Radio-Therapy (CONVERT) trial. Patients were randomized to receive 45 Gy/30 twice-daily fractions/19 days or 66 Gy/33 once-daily fractions/45 days concurrently with platinum-based chemotherapy [71 90].

Neutropenia grade 3/4 occurred more frequently in the elderly (84 *versus* 70%; $p = 0.02$) but rates of neutropenic sepsis (4 *versus* 7%; $p = 0.07$) and death (3 *versus* 1.4%; $p = 0.67$) were similar in both groups. With a median follow-up of 46 months; median survival and median time to progression in the elderly versus younger groups were not statistically significant. In elderly patients with good PS (0-2) less-intensive treatment (e.g. single-agent etoposide) is inferior to combination chemotherapy (e.g. platinum plus etoposide). Furthermore, future researches should focus on predictive patient characteristics to distinguish patients within the heterogeneous older population who can benefit from curative-intent treatment [91].

ROLE OF IMMUNE CHECKPOINT INHIBITORS IN ADVANCED DISEASE

The improvement in the knowledge of the biology of both NSCLC and SCLC, the discovery of targetable oncogenic drivers and the availability of new effective drugs for actionable mutation has dramatically changed in recent years the therapeutic scenario of patients with LC [92-101]. In particular, recently, a new therapeutic approach based on targeting the immune checkpoints (IC) has been introduced. ICs include complex regulatory pathways which maintain the balance between the appropriate recognition and destruction versus pathogens and tumors, and the inappropriate overstimulation of immune responses, which leads to autoimmunity. These regulatory pathways involve both costimulatory and co-inhibitory factors which fine-tune the antigen specific T-cell response after stimulation of the T-cell receptor [102 103]. Molecules involved in tuning the immune system include: PD-1 (programmed cell death protein-1) or its' ligand (PDL-1) and CTLA-4 (cytotoxic T-lymphocyte-associated antigen-4). The binding between PD-1 and its ligand, which may be expressed on the cancer cells surface, inactivates the T cell response. Immune checkpoint inhibitors (ICIs) blocking PD-1 (Nivolumab and Pembrolizumab) or PD-L1 (Durvalumab, Atezolizumab, Avelumab) have already been approved for treatment of advanced NSCLC or are in late stages of development. Unfortunately, the elderly population is generally underrepresented in NSCLC clinical trials and most of the evidence arises from selected study population. A recent systematic review, although not specific to NSCLC, compares the activity of ICIs in the young and in the elderly patients [104]. Nine RCTs of ICIs (ipilimumab, tremelimumab, nivolumab and pembrolizumab) were evaluated, including 5265 patients, divided using a variable cut off of 65 or 70 years depending on the study considered. The results showed an improvement in the OS in both groups, compared to standard chemotherapy (young patients: HR, 0.75; 95% CI, 0.68-0.82; older patients HR, 0.73; 95% CI, 0.62-0.87). Also, PFS analysis showed an improvement in both groups of patients (young patients: HR, 0.58; 95% CI, 0.40-0.84; elderly patients: HR, 0.77; 95% CI, 0.58-1.01). Furthermore, though ICIs showed a safe toxicity profile in NSCLC, the knowledge about toxicity in elderly population of these molecules is limited because most of ICIs studies have involved a low number of elderly patients. The immune-related adverse events (irAEs) are defined as idiosyncratic adverse events to ICIs and may be more challenging in elderly patients due to reduced functional reserve, age-associated comorbidities and co-medications. Drug-related adverse events of special interest such as

hypothyroidism, rash, pneumonitis, increased alanine and aspartate aminotransferase levels were observed in clinical trials.

CONCLUSIONS

LC management in older subjects is not straightforward for clinicians as the reduced functional reserve coupled with the comorbidities influence both the diagnostic and therapeutic choices. When feasible, surgery represents the mainstay of the treatment and promising results have been shown in elderly patients. In advanced disease, the elderly population is often under-represented in clinical trials and the correct management is still an object for debate. Immunotherapy appears to demonstrate promising results in subsets of patients in clinical trials coupled with a favourable safety profile. However, irAEs in the older subjects could be more challenging in patients with comorbidities and further observations are required to establish best practice in LC elderly population.

Conflict of interest

The Authors have no conflict of interest to declare.

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