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Management of Metastatic Nonsmall Cell Lung Cancer in Elderly

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Abstract

There is limited data on management of metastatic nonsmall cell lung cancer (NSCLC) in the elderly population due to lack of representation of this subset in clinical trials. The projected representation of elderly population of patients globally is expected to rise significantly in the years to come. It is imperative to understand the specific challenges and opportunities in management of elderly with NSCLC. Even in the elderly, the medical management of advanced NSCLC begins with driver mutation testing on lung biopsy. Once the patient is classified as driver mutation positive or negative, they can either be treated with a single-agent-targeted therapy or with immunotherapy and chemotherapy or after programmed death ligand 1 (PDL-1) assessment, with immunotherapy alone. After starting the appropriate therapy, the disease needs to be monitored at every 3 months with reassessment scans. Treatment in elderly should be designed as per their functional and not chronological age, and geriatric assessment scales should be utilized wherever possible to understand the functional age of the patient.

Keywords
- elderly
- lung cancer
- functional age
- geriatric assessment scale

Introduction

Lung cancer is the second most common cancer and the leading cause of mortality related to cancer, irrespective of sex. It is expected that in 2020, nearly 228,820 adults (116,300 men and 112,520 women) will be diagnosed with lung cancer in the United States. Thirteen percent of all newly diagnosed cancers comprise of lung cancers. In recent years, however, the incidence of lung cancer has plummeted among men and women by 3 and 1.5%, respectively. The 5-year survival rate for lung cancer (including small cell lung cancer [SCLC] and non-SCLC [NSCLC]) is around 19% with men having a lower survival rate when compared with their female counterpart.[1] Age has a strong correlation with lung cancer mortality rate, with higher mortality in elderly patients irrespective of their sex. The incidence of lung cancer directly correlates with age as well, with 6% incidence rate is seen in patients 50 years or younger, 29% among patients between the age of 60 and 69 years, and 44% among patients 70 years or older.[2] There is limited data on treatment of advanced lung cancer in the elderly due to lack of representation of this subset in clinical trials. The projected representation of elderly population of patients globally is expected to go up to more than 2 billion by year 2050 and is expected to represent 7.2% of Indian population by the year 2025.[3] Although the data regarding representation of elderly in the new cancer patient

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pool in India is limited, in a single-center observational study at a radiotherapy center, elderly patients above 60 years of age formed 28% of the total new patient population receiving radiation.[4] In another study looking at patterns of cancer care in the elderly (patients above 70 years of age), nearly 23% of patients were with lung cancer and half of the total cohort of patients received curative therapy where geriatric assessment tool was found to be meaningful for better characterization of these patients.[5] A third study at a tertiary center looked at toxicity from chemotherapy in the elderly defined as patients above 56 years of age. Sixty-four percent of these patients were found to be able to complete their prescribed chemotherapy protocols which is remarkable.[6] This underscores the fact that it is imperative to understand the specific challenges and opportunities in treatment of elderly, preferably with help from geriatric assessment tools to offer optimal therapy in this population.

Lung cancer is broadly classified into SCLC and NSCLC.[1,7] NSCLC can be further classified into adenocarcinoma, squamous cell carcinoma, large cell carcinoma, and NSCLC undifferentiated or NSCLC not otherwise specified (NOS). In the recent times, lung cancer is also divided into driver mutation negative and driver mutation positive lung cancer. Most driver mutations are seen in lung adenocarcinomas. The most frequently tested mutations are epidermal growth factor receptor (EGFR), antiplastic lymphoma kinase (ALK), ROS1, and BRAF in both lung biopsies and venous blood samples or liquid biopsies.[1,8] The presentation of mutations (the most common being EGFR) varies widely depending on ethnicity (around 10% adenocarcinoma lung patients in the United States have EGFR mutation versus 30 to 50% in Asian patients with adenocarcinoma lung).[8,9] For patients who are driver mutation negative, novel treatments with chemotherapy with or without immunotherapy have developed.

Challenges in Elderly Population

When compared with their younger counterparts, elderly NSCLC patients have reduced capability of performing activities of daily living (ADL) and instrumental ADL (IADL). The risk for chronic obstructive pulmonary disease (COPD) and cumulative effect of smoking increases with age further compromising pulmonary function.[10] Elderly lung cancer patients are more likely to have cardiac comorbidities, such as congestive cardiac failure (CCF), which presents a challenge while considering chemotherapies that require high-volume hydration during administration.[11] Other organs are also affected with increasing age. Creatinine clearance slows down significantly with increase in age, thus requiring dose adjustment for therapy that are cleared through the kidneys (cisplatin being one example).[12] Also, hepatic metabolism of the drug is compromised in part due to decreased rate of cytochrome P450 enzyme metabolism.[13] This combined with the compromise in renal clearance will lead to persistently high levels of cytotoxic drugs in the blood and increased toxicities.

The immune system undergoes a gradual decline with age which leads to increased susceptibility and decreased ability to respond to various diseases including cancer. This process is known as immunosenescence which affects both innate immunity, as well as adaptive immunity. Innate immunity, in spite of being relatively stable throughout one's lifetime, has shown a decrease in function of antigen presenting cells (APCs), especially dendritic cells and a decrease in cytotoxic potential with respect to natural killer cells (NK cells) with age.[14] In terms of adaptive immunity, there is a reduced development and total number of B- and T-cells.[15-17] An overall decrease in the number of naïve CD4+ and CD8+ T-cells leads to decrease in the individual's ability to mount a cell-mediated immune response to new antigens especially from tumor microenvironment. Immunosenescence is one of the factors to keep in mind when considering treatment in elderly with immunotherapy either as a monotherapy or in combination with chemotherapy and chemotherapy alone.

Apart from physiological challenges, psychosocial distress is a growing concern among elderly suffering from cancer. More than 25% lung cancer patients suffer from either depression or anxiety, most frequently seen at the time of diagnosis, due to treatment-related misconceptions, on disease progression and near the end of life. Along with psychiatric disorders, social aspects, including poor support system, loss of independence, financial burden, and misinformation regarding prognosis and treatment options,[18] are seen more frequently among elderly when compared with their younger counterparts. It is important to not only evaluate physical wellbeing but also access the psychosocial factors among elderly NSCLC patients.

Special attention should be paid to the blood tests done in elderly since age-specific reference ranges may not be utilized in the report generation, flagging off blood test results as abnormal, or out of reference incorrectly. Blood test results in elderly should be interpreted with caution and only essential tests should be ordered to reduce misinterpretation due to false positives and false negatives.[19,20]

Chronological Age versus Functional Age

Aging, an inevitable process, is often an interpretation of the chronological age and, as is norm, a person aged 65 years or more is often referred to as "elderly."[21] However, even among patients with a similar chronological age, the functional or physiological status varies significantly which in turn influences the tolerance and survival of elderly patients on various treatment modalities. Chronological age is merely a number, whereas functional age depicts the cumulative effect of medical and psychosocial stressors (e.g., caregiving or loss of independence) on the aging process that may affect life expectancy.[22] Oncologists commonly use subjective scales, such as the Eastern Cooperative Oncology Group (ECOG), Karnofsky performance status scales, ADL, and IADL, to determine the functional status of individuals.

Screening tests that determine if the patient will benefit from geriatric assessment tools are commonly deployed in busy clinical setting. The most widely used screening tools are the G8, Vulnerable Elders Survey-13 (VES-13), and Flemish version of the Triage Risk Screening Tool (TRST).[23-25] Geriatric assessment tools, such as the Cancer and Aging Research

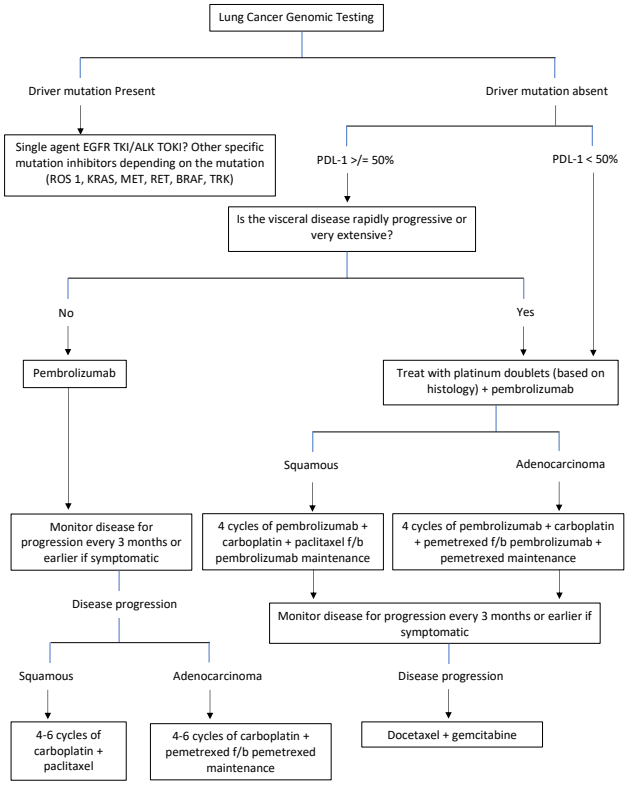
Group (CARG) and Prediction Tool and the Chemotherapy Risk Assessment Scale for High-Age Patients (CRASH), were developed to assess risk to benefit ratio of a multitude of treatment of options. The CARG model, takes into consideration variations in geriatric assessment; laboratory test; and patient, tumor, and treatment characteristics, to estimate the risk of developing severe toxicity from cancer treatment. A score of 0 to 5 is low risk, 6 to 9 is mid risk, and 10 to 19 is high risk for toxicity from chemotherapy. The CRASH model, on the other hand, considers the specific chemotherapy regimen used, laboratory tests, and assessment tools, such as the ECOG performance status, Mini-Nutritional Assessment, and Mini-Mental State Examination (MMSE; to assess the functional, nutritional, and mental status, respectively), to predict the risk of grade 3 or higher chemotherapy-related toxicities.[22]

Comprehensive geriatric assessment (CGA) consists of a set of tools for assessing cognitive function; psychological, functional, and nutritional status; comorbidities (assessed with the Charlson comorbidity index and the Cumulative Illness Rating Scale for Geriatrics [CIRS-G]); and medication. Many clinicians have, however, questioned its significance in treatment decision-making due to it is being time consuming, cumbersome, and subjective.[26] A pooled analysis of two studies found that among all of CGA's components only performance status and comorbidities play a significant role in determining the overall survival of elderly with NSCLC.[6]

Keeping all this in mind, it is important to use a combination of geriatric assessment tools, performance status scales and assessment of ADL, IADL, and MMSE to fine tune specific treatment therapies on individual basis. A quick screening tool, like G8 or VES-13 or TRST, could be utilized to triage patients for full comprehensive geriatric assessment tool assessment which is a much more involved process that could take nearly 40 minutes to deliver and is used for evaluation, as well as treatment in the elderly.

Treatment Options

Even in the elderly, the medical management of advance NSCLC begins with driver mutation testing on lung tissue biopsy or liquid biopsy after the diagnosis has been confirmed. Once the patient is classified as driver mutation positive or negative, they can either be treated with single-agent-targeted therapy or with immunotherapy and chemotherapy or immunotherapy alone for programmed death ligand 1 (PDL1) >50%. After starting the appropriate therapy, the disease needs to be monitored at every 3 months with reassessment scans. A summary of suggested protocols is described in ►**Fig. 1**.



ALK – aplastic lymphoma kinase, EGFR – epidermal derived growth factor receptor, f/b – followed by, KRAS – Kirsten rat sarcoma viral oncogene, PDL-1 – programmed death ligand - 1, RET – rearrangement during transfection, TKI - tyrosine kinase inhibitor.

Fig. 1 Summary of treatment protocol. ALK, antiplastic lymphoma kinase; EGFR, epidermal growth factor receptor; f/b, followed by; KRAS, Kirsten rat sarcoma viral oncogene; PDL1, programmed death ligand 1; RET, rearrangement during transfection; TKI, tyrosine kinase inhibitor.

Driver Mutation Positive

Epidermal Growth Factor Receptor Inhibitors

Treatment with EGFR tyrosine kinase inhibitors (TKIs) (osimertinib, afatinib, erlotinib, and gefitinib) as a monotherapy is indicated for the initial treatment of patients who are diagnosed with EGFR mutation positive NSCLC. This is preferred over chemotherapy- and immunotherapy-based approaches for patients with an identified driver mutation. A pooled analysis of 456 citations shows that the overall pooled prevalence for *EGFR* mutations was 32.3% with ethnicity playing a considerable role in the prevalence of the disease, ranging from 38.4% in Chinese population to 14.1% in Europeans. The data also showed a higher pooled prevalence in female patients (females vs. males: 43.7 vs. 24.0%), nonsmokers or light smokers (nonsmokers or light smokers vs. patients with a history of heavy smoking: 49.3 vs. 21.5%), and patients with adenocarcinoma of the lung (adenocarcinoma vs. nonadenocarcinoma: 38.0 vs. 11.7%).[27]

Both erlotinib and gefitinib have shown improvement in overall response rate (ORR) and disease control rate (DCR) among elderly with EGFR mutation. When comparing them to younger demographic patients, the progression-free survival (PFS) and overall survival (OS) are similar or better, suggesting a strong role of EGFR inhibitors in the treatment of NSCLC with EGFR mutation. The overall toxicity was higher among elderly but was well tolerated with only a handful of patients having to withhold therapy due to adverse events. The above-mentioned studies also suggested that gefitinib was slightly better tolerated than erlotinib in elderly population with lower rates of grade 3 and higher toxicity.[28-31] In a large phase-III study, gefitinib with chemotherapy was shown

to be superior to gefitinib alone for EGFR-positive advanced lung adenocarcinoma, and although the study had limited elderly representation, the regimen was as efficacious in the elderly as the younger population. However, the details regarding tolerability and quality of life are not available to comment on.[32] The most common side effects are diarrhea, rash, and fatigue which could be managed with prophylactic use of antidiarrheals, antihistaminic ointments, and antiallergics, and may sometimes require dose reductions.

Interestingly, a recent phase-II clinical trial that included elderly and frail patients diagnosed with EGFR-positive NSCLC treated with low-dose erlotinib (50 mg/day) to understand the overall outcome of the disease, as well as development of toxicity. The results were favorable with fewer patients developing grade 3 and higher toxicity and no reported treatment-related deaths. Median PFS and OS were better than studies that used standard dose of erlotinib (150 mg/day).[33] This suggests a role of dose adjustment in elderly with NSCLC treated with EGFR inhibitors but awaits further confirmation.

Second-generation TKI afatinib is known to have a higher toxicity and dose reductions are common. A post hoc analysis of the GIDEON trial, a phase-III study, was conducted to look at safety and efficacy of afatinib in the elderly over 70 years of age that represented 44% of the total patients included in the study. The analysis showed that the ORR, PFS, and safety with afatinib was comparable in the elderly to the younger population. The rate of dose reductions was also similar in elderly versus the younger patients but there was slightly higher trend starting at 30-mg daily dose in the elderly >70 years than <70 years.[34]

Third-generation TKI osimertinib is approved for upfront EGFR inhibition, as well as targeting the T790M mutation, a mutation identified in EGFR resistant cases after prior exposure to first- or second-generation TKIs. A study which included a subset of elderly patients with EGFR T790M mutation showed promising results with ORR and PFS that matched that seen in younger patients.[35] The details of the trials are included in ►**Table 1**.

Our recommendation for EGFR inhibition in elderly is to offer similar drugs as in younger patients. The first-line option of treatment would still be considered osimertinib, especially for patients presenting with brain metastasis. For those patients who are unable to access osimertinib, the recommendation would be considered to reduce dose of afatinib. Gefitinib with chemotherapy could also be an option for fit elderly patients. A geriatric assessment tool should be utilized to finalize the regimen and the dosage of these medications,

Table 1 Summary of studies involving targeted therapy in the treatment of elderly with NSCLC

Study name	Targeted therapy agent	Median age in years	Response	Toxicity
BR21[28]	Erlotinib 150 mg	≥70 vs. <70	PFS: 3 vs. 2.1 months. OS: 7.6 vs. 6.4 months	Severe toxicity grades 3 and 4: 35 vs. 18%
TaRceva LUng cancer Survival Treatment (TRUST)[29]	Erlotinib 150 mg	>70 vs. general TRUST population	DCR: 79 vs. 69% PFS: 4.5 vs. 3.2 months OS: 7.3 vs. 7.9 months	18% in elderly (not significantly different)
Single-arm phaseII trial with the Southwest Oncology Group (SWOG)[33]	Erlotinib 50 mg (low dose)	80	ORR: 60% DCR: 90% PFS: 9.3 months OS: 26.2 months	Grade 3 and higher: 5%
Multicenter phase-II study[30]	Gefitinib 250 mg	20 to 74 years of age with ECOG PS 3 and 4, 75–79 years of age with PS 2–4, and ≥80 years of age with PS 1–4	ORR: 66% DCR: 90% PS improvement rate: 79% PFS: 6.5 months	–
The Nagano Lung Cancer Group study[31]	Gefitinib 250 mg	≥75	ORR: 59% DCR: 88% PFS: 12.9 months	Grade-3 toxicity: 13%
The Central Japan Lung Study Group 0901[32]	Gefitinib 250 mg	79.5	ORR: 70% DCR: 90% PFS: 10 months OS: 26.4 months	Grade 1: 5%
The Institutional Review Board of the Aichi Cancer Center, Japan[35]	Osimertinib	≥75 vs. <75	ORR: 61.1 vs. 50.8% PFS: 17.7 vs. 10.5 months	Grade 2 and higher paronychia: 16.6 vs. 1.6% Overall AE: no significant difference
NCT00585195[39]	Crizotinib 250-mg twice daily	≥65 vs. <65	ORR: 65 vs. 62.5%	–

Abbreviations: AE, adverse effect; DCR, disease control rate; NSCLC, nonsmall cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival;ECOG PS, Eastern Cooperative Oncology Group performance score.

especially for first- and second-generation TKIs, mainly due to slightly higher rates of toxicity with these generations than with osimertinib. First-generation TKIs, like gefitinib and erlotinib alone, could also be utilized in frail and elderly and has been known to provide disease control and survival advantage.

Antiplastic Lymphoma Kinase Inhibitors

The *ALK* gene is located on chromosome 2 and encodes a transmembrane tyrosine kinase. Also, 2 to 5% of NSCLC patients have ALK rearrangement. It is more often seen in light of nonsmoker male patients of younger age group.[36] Limited data exist when it comes to ALK inhibitors being used in elderly since this mutation is often seen in the younger population.

Individual case reports exist which have shown effectiveness of crizotinib in ALK and ROS1 mutation.[37,38] A study with limited number of elderly patients diagnosed with NSCLC showed similar ORR in elderly when compared with <65 years' subset.[39] The results of a subgroup analysis of the ALEX study, which compared the efficacy of first-generation TKI crizotinib and third-generation TKI alectinib as first-line therapy in patients younger than 65 years to those older than 65 years, showed similar benefits in both age groups in terms of median PFS, with the alectinib group having a better overall outcome than the crizotinib. An analysis of the J-ALEX study that focused on the Japanese demographic also showed similar results.[40]

Ceritinib is a second-generation TKI which targets ALK kinase receptor. Although it does not have MET inhibitor activity, it also targets insulin-like growth factor 1 receptor (IGF-1R), insulin receptor (InsR), and ROS1. Two phase-III studies, ASCEND-4 and ASCEND-5, compared ceritinib to chemotherapy (pemetrexed or docetaxel) in first- and second-line therapy, respectively. This study, however, was not aimed toward comparing elderly patients to younger patients. Subset analysis showed no significant difference in benefit between the younger and elderly subgroups. Further studies are needed to ascertain the role of ceritinib in elderly population.[41,42]

Our recommendation would be considered the same drugs for ALK inhibition for the elderly as for the younger population, with alectinib as the drug of choice as first line, or ceritinib for those who have difficulty accessing alectinib. Crizotinib is the most economical option and still remains a practical option for those who cannot afford the second- and third-generation TKIs.

Other Driver Mutations

The ROS1 mutation is a mutation occurring in the *ROS1* oncogene on chromosome 6, resulting in a defective receptor tyrosine kinase which has structural similarity to the ALK. ROS1 rearrangement is seen in 1 to 2% of NSCLC patients. A case report by Overbeck et al showed a 90-year-old male with ROS1 rearrangement NSCLC having partial response to crizotinib.[38] Even though data exist that proves the efficacy of ALK TKI against ROS1-mutated NSCLC patients,[43,44] there is limited data centered around elderly population and further studies may provide further understanding of treatment options in this subset.

Although there is significant limitation to data with regard to outcomes in elderly with novel target therapy drugs due to lack of clinical trial participation, several case reports and anecdotal data describe similar response to treatment in these patients. A 70-year-old Asian female with BRAF-mutated NSCLC had excellent response to dabrafenib and trametinib combination therapy.[45] In another case series of BRAF-mutated lung cancer patients with a median age of 68 years, the patients had similar efficacy and toxicity reported with vemurafenib in comparison to the historical data.[46]

With molecular tests becoming more frequently available, the chances of the elderly being detected with a rare potentially targetable mutation are increasing. We recommend to look at the most current data whenever offering novel targeted therapeutic options to patients older than 65 years of age with special attention to safety. Assessment of the functional status with geriatric assessment tools would help plan the therapy better.

Driver Mutation Negative

Chemotherapy

Elderly patients who are ineligible for targeted therapy or immunotherapy could be offered chemotherapy as a single agent or as combination chemotherapy. Results of various trials are included in ►**Table 2**.

Single-Agent Chemotherapy

Till the late 90s, cancer therapy for NSCLC, especially in the elderly population, largely consisted of supportive care. However, this notion was changed with the Elderly Lung Cancer Vinorelbine Italian study (ELVIS) which showed significant benefit of using vinorelbine for treatment of NSCLC in elderly.[47] This was followed by the Japanese study by Kudoh et al, WJTOG9904, that showed docetaxel prolonged OS and PFS in elderly with NSCLC when compared with vinorelbine. This led to docetaxel being accepted as a single-agent chemotherapy of choice for the elderly in Japan for many years.[48]

Combination Chemotherapy

Later, combination platinum-based chemotherapy was studied in the elderly population that would soon be accepted as a standard regimen for treatment of NSCLC. A meta-analysis of the Cochrane Database of Systematic Review on 51 clinical trials showed an improvement in terms of median OS with chemotherapies combined with a platinum agent compared with nonplatinum agent in elderly patient subgroup; however, the toxicity also tended to worsen.[49] Intergroupe Francophone de Cancerologie Thoracique (IFCT)—0501—compared the safety and efficacy of combination carboplatin and paclitaxel to that of single-agent vinorelbine or gemcitabine. The study showed a prolonged survival in elderly patients on platinum-based doublet therapy compared with single-agent chemotherapy. However, Grade 3 and 4 toxicities were pronounced in the combination therapy.[50] A pooled analysis of MILES 3 and MILES 4, along with JCOG0207, studied the safety and efficacy of cisplatin in combination with other

Table 2 Summary of studies involving chemotherapy (single agent and combination) in the treatment of elderly with NSCLC

Study name	Chemotherapy agent	Median age (years)	Response	Toxicity (grades 3 and 4)
ELVIS[47]	Vinorelbine vs. the best supportive care (BSC) vs. vinorelbine + gemcitabine	>70	OS: 6.5 vs. 4.9 vs. 7.6 months	18%
WJTOG9904[48]	Vinorelbine 25 mg/m^2 (days 1 and 8) vs. docetaxel 60 mg/m^2 (day 1)	76	ORR: 9.9 vs. 22% OS: 9.9 vs. 14.3 months PFS: 3.1 vs. 5.3 months	69.3 vs. 82.9%
IFCT-0501[50]	Carboplatin + paclitaxel vs. vinorelbine/gemcitabine	77	ORR: 27.1 vs. 10.2% OS: 10.3 vs. 6.2 months PFS: 6 vs. 2.8 months	48.4 vs. 12.4%
MILES 3 and MILES 4[73]	Cisplatin + gemcitabine/ pemetrexed vs. single-agent gemcitabine/pemetrexed	75	ORR: 15.5 vs. 8.5% OS: 9.6 vs. 7.5 months PFS: 4.6 vs. 3 months	Significantly higher and more severe in patients on cisplatin
JCOG0207[74]	Cisplatin 25 mg/m^2 on days 1, 8, and 15 + docetaxel 20 mg/m^2 vs. docetaxel 20 mg/m^2	76	ORR: 55 vs. 26.2% OS: 17 vs. 10.7 months PFS: 6.2 vs. 3.7 months	14.3 vs. 4.8%
Socinski et al[53]	Nab paclitaxel 100 mg/m^2 weekly + carboplatin vs. paclitaxel 200 mg/m^2 every 3 weekly + carboplatin	≥70	ORR: 34 vs. 24% OS: 8 vs. 6.8 months PFS: 19.9 vs. 10.4 months	55 vs. 73%
NCT01836575[51]	Pemetrexed 500 mg/m^2 + carboplatin AUC 5 vs. pemetrexed 500 mg/m^2 alone	≥70	OS: 9.9 vs. 5.3 months	11.7 vs. 3.8%
PARAMOUNT[52]	Pemetrexed 500 mg/m^2 maintenance vs. placebo (both groups received pemetrexed 500 mg/m^2 + cisplatin 75 mg/m^2 initial therapy for four cycles)	73	ORR: 42 vs. 43% OS: 13.7 vs. 12.1 months PFS: 6.4 vs. 3 months	17% vs. nil

Abbreviations: AUC, area under curve; NSCLC, nonsmall cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival.

cytotoxic chemotherapy compared with monotherapy in elderly NSCLC patients. The combination therapy yielded prolonged PFS, however, showed significantly higher grade 3 and 4 toxicities which question how well cisplatin will be tolerated in the elderly and frail population.

Pemetrexed along with carboplatin was compared with pemetrexed monotherapy by Zukin et al for the treatment of NSCLC. In the elderly subset (≥70 years), they saw a benefit, in terms of OS, with combination therapy, even though there was a slight increase in the incidence of grade 3 and 4 toxicities.[51] PARAMOUNT trial compared maintenance treatment with pemetrexed to placebo in elderly who had initially received four cycles of combination cisplatin and pemetrexed. An overall improvement in PFS was observed; however, toxicity was observed with pemetrexed maintenance.[52]

Nab paclitaxel in combination with cisplatin was compared with solvent-based paclitaxel in combination with cisplatin in elderly NSCLC patients by Socinski et al,[53] PFS and ORR were improved, even though OS was similar, with nab paclitaxel combination along with lower rates of grade 3 and 4 toxicities.

Our recommendation for chemotherapy in elderly is to first assess them with geriatric assessment tool for their functional capacity. Those patients with good functional capacity should be treated with combination of platinum-based chemotherapy followed by maintenance doses as tolerated, based on histopathology of the cancer, and those that are frail could be offered single-agent chemotherapy like nab-paclitaxel, vinorelbine, or single-agent pemetrexed.

Immunotherapy

Ever since pembrolizumab received Food and Drug Administration (FDA) approval for treatment of metastatic NSCLC in patients who progressed on platinum based chemotherapy or targeted therapy as applicable, researchers and clinicians have pursued to understand the role of immunotherapy in the treatment of elderly. Biomarkers, like PDL1 and TMB, are utilized to decide the appropriate regimen. High PDL1 ≥ 50% more frequently and seldom high TMB are classically biomarkers where single-agent immunotherapy could be offered.[6] Initially, the notion of immune-related adverse event (irAEs) and development of immunosenescence have been of concern for the elderly. However, recent studies have shown promising results. A pooled analysis from institutional database on NSCLC patients treated with immunotherapy compared response and adverse events in <70 years, 70 to 79 years, and >80 years of subgroups found no significant change in OS, as well as no significant increase in irAEs among elderly population.[54]

When comparing data from CHECKMATE 171 and CHECKMATE 153 treatment-experienced patients aged 70 years or older with advanced NSCLC managed with nivolumab, analysis demonstrated similar survival outcome

between the overall population and elderly patients without any significant increase in irAEs in elderly subgroup. These two studies also included patients with ECOG PS 2 and higher but the results were not favorable. Patients with ECOG performance score (PS) 2 and higher had a shorter median OS.[55,56] OAK trial compared atezolizumab to docetaxel in NSCLC patients. The elderly subgroup (≥65 years) had favorable outcome to atezolizumab when compared with docetaxel with significantly extended OS and markedly lower rates of grade 3 and 4 toxicities.[57]

A pooled analysis by Nosaki et al using data from KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 showed that in elderly subset on pembrolizumab for treatment of NSCLC had improved OS when compared with chemotherapy. Also those who had PDL1 tumor proportion score (TPS) higher than 50%, also had a significantly extended OS while on pembrolizumab with significantly lower grade 3 and 4 adverse events. By comparing outcomes in terms of age, older patients with a PDL1 TPS ≥50% appeared to have a more favorable outcome from pembrolizumab than younger patients. However, in elderly population, higher incidences of infusion reactions was observed compared with the younger population.[58]

Most elderly patients would be candidates for immunotherapy and routine exclusion criteria should apply. From the review of the available data, the efficacy of immunotherapy in good performance status elderly would be similar to the general patient pool with minimal safety concerns like some incidences of infusion reactions in the elderly. Poor performance status is an independent variable of concern across all ages but especially in the elderly and performance status assessment and geriatric assessment tools remain the mainstay of delivering nuanced care in the elderly population. A summary of trials in this space is enlisted in ►**Table 3**.

Antivascular Endothelial Growth Factor Treatment

Bevacizumab received FDA approval for treatment of NSCLC along with carboplatin and paclitaxel combination. In the elderly population, however, bevacizumab is associated with high rates of severe adverse events and treatment-related deaths. The data from subset analysis of the ECOG4599 trial and pooled analysis of the PointBreak trial showed that bevacizumab had no additive interaction when combined with cytotoxic chemotherapy in elderly NSCLC patients; however, the toxicity was increased dramatically.[59] On analyzing the subgroup data of the REVEL trial, the additive interaction of ramucirumab to docetaxel was not observed in elderly patients, and the incidence of severe adverse events tended to be higher in the combination group.[60]

We think that the above data strongly suggest that antivascular endothelial growth factor (anti-VEGF) therapy with or without cytotoxic chemotherapy is challenging for the elderly and could be best avoided or given with caution in the relatively fit elderly patients with specific indications.

Role of Palliative Care

Palliative care integrates symptomatic management with supportive aid in terms of psychosocial and treatment decision-making faced by the patients and their caregivers. When administered concurrently with the current therapeutic strategies, it is known to improve patient's quality of life, as well as OS.[61,62] Pain control remains one of the most important issues to tackle in cancer patients, especially lung cancer. Studies have shown a pain prevalence rate of 75 to 90% in patients suffering from lung cancer.[63] The World Health Organization's (WHO) analgesic ladder for cancer pain relief has laid down guidelines which remain the cornerstone for management of pain in cancer patients.

Table 3 Summary of studies involving immunotherapy in the treatment of NSCLC in elderly[51]

Study name	Immunotherapy agent	Median age (years)	Response	Toxicity (grades 3 and 4)
Institutional database[54]	Anti PD1/anti-PDL1/CTLA 4 inhibitor	<70 vs. 70–79 vs. >80	ORR: 21.5 vs. 22.3 vs. 18.8% OS: 9.1 vs. 11.3 vs. 9.6 months PFS: 2.8 vs. 3.5 vs. 2.6 months	35.8 vs. 32.7 vs. 37.5%
CHECKMATE 171[55]	Nivolumab	≥70 vs. ≥75 vs. ECOG PS 2	OS: 10 vs. 11.2 vs. 5.6 months	12 vs. 14 vs. 6%
CHECKMATE 153[56]	Nivolumab 3 mg/kg	Overall population vs. ≥70 vs. ECOG PS 2	OS: 9.1 vs. 10.3 vs. 4 months	4–5% in all groups
OAK trial[57]	Atezolizumab 1,500 mg vs. docetaxel 75 mg/m^2	65	OS: 13.8 vs. 9.6 months	15 vs. 43%
KEYNOTE 010, 024, 042 pooled analysis[58]	Pembrolizumab vs. chemotherapy	≥75	OS: 15.7 vs. 11.7 months (note those with PDL-1 TPS ≥50% had OS of 23.1 months on average)	24.2 vs. 61%

Abbreviations: CTLA 4, cytotoxic T-cell associated protein 4; ECOG PS, Eastern Cooperative Oncology Group performance score; NSCLC, nonsmall cell lung cancer; ORR, objective response rate; OS, overall survival; PDL1, programmed death ligand 1; PFS, progression-free survival; TPS, tumor proportion score.

The range of options in their order of use include nonsteroidal anti-inflammatory drugs (NSAIDs), weak opioids, and stronger opioids.[64] Patients with NSCLC experience dyspnea in more than 50% cases.[65] Depending on the etiology (tumor invasion, mainstem bronchus obstruction, and chemotherapeutic side effect), palliative interventions, like bronchoscopy, laser therapy, stent placement, and endobronchial brachytherapy, could be used. Pleural effusion could be tackled with palliative thoracocentesis. Supportive treatments, like supplemental oxygen, bronchodilators, opioids, pulmonary physiotherapy, and systemic steroids, could be utilized to improve the morbidity.[66]

Early palliative intervention has been shown to enhance quality of life and enhance survival and is recommended in all but especially the elderly due to the special needs present in this patient population.

Palliative Radiotherapy and Other Feasible Options

For patients with locally advanced lung cancer who are not eligible for surgical resection or for patients with metastatic disease with severe respiratory symptoms (atelectasis, severe shortness of breath, mainstem bronchus obstruction/severe wheezing, superior vena cava obstruction or SVC syndrome, hemoptysis, severe dysphagia, and chest pain), palliative radiotherapy to the lung has shown improvement symptomatically and in quality of life. Palliative radiotherapy is a viable treatment option for bone, brain, subcutaneous, lymph nodes, or pulmonary metastases. However, due to poor tolerance among elderly population, stereotactic body radiation therapy (SBRT) and stereotactic radiosurgery (SRS) have taken center stage in the treatment of metastatic NSCLC.

SBRT is the standard of care for patients who are inoperable. Kreinbrink et al conducted a study with limited number of patients with median age of 84 years suffering from early-stage NSCLC treated with SBRT. They found SBRT with BED of ≥100 Gy10 is extremely safe, highly effective, and has inordinately low toxicity rates (0 grade 2–5 toxicities).[67] A multicenter study reported 34% patients developed grade-2 toxicity but none developed grade 4 and 5 toxicities.[68] In the phase-II clinical trial Stereotactic Ablative Radiotherapy for Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET) comparing standard palliative radio therapy to SBRT or SABR in elderly NSCLC patients with up to five metastases showed improvement in OS (28 vs. 41 months).[69] SBRT is considered safe and effective in elderly patients with early-stage NSCLC and given its convenience and high therapeutic ratio, it should be considered in advanced NSCLC.[69] Endobronchial brachytherapy, endobronchial laser therapy, and endobronchial stenting are other palliative measures that are seldom utilized for palliation of disease.[70]

For elderly and frail patients with brain metastasis, SRS is a viable option. A study by Minniti et al observed the safety and efficacy of SRS in NSCLC patients ≥70 years with up to four metastatic brain lesions[71] and 1- and 2-year local control rates were 90 and 84%, respectively, with a median survival of 13.2 months. This data seems promising, especially when compared with whole brain radiation therapy (WBRT) where the median survival is much shorter with significant morbidity posttreatment.[72]

We recommend that palliative radiation could be utilized on a case-by-case basis in the elderly for symptom control and for the management of brain metastasis. Whole brain radiation remains the standard of care therapy for brain metastasis; however, wherever deemed appropriate, SRS could be utilized in place of WBRT, especially in the elderly, to help preserve cognitive function and quality of life.

Conclusion

1. Chemotherapy-related therapeutic decisions in elderly NSCLC patients should be personalized based on geriatric assessment tools, as it correlates with toxicities and OS. It is essential to focus on functional status rather than chronological age while making treatment decisions.
2. Driver mutations should be recognized wherever indicated for improved results and to minimize the need for chemotherapy.
3. For elderly patients with no driver mutation, immunotherapy has shown superior efficacy in elderly with advanced disease and should be considered as monotherapy in all patients with PDL1 TPS 50% or higher.
4. The elderly patients who are driver mutation negative and PDL1 TPS <50% or negative would not be eligible for upfront targeted therapy or single-agent immunotherapy and should be offered either chemotherapy alone or in combination with immunotherapy where applicable. Carboplatin-based doublet therapy demonstrates clear survival advantage compared with monotherapy, although with a greater toxicity risk. Among single-agent chemotherapy, pemetrexed (in nonsquamous cell cancers) and nab paclitaxel have shown efficacy with improved safety and should be considered in patients with poor ECOG PS. A comprehensive geriatric assessment should be performed before finalizing recommendations.
5. The addition of bevacizumab to chemotherapy in elderly patients appears to be associated with additional toxicity, especially in patients aged 75 years and older and is best avoided or should be given with extreme caution.
6. In elderly patients with no driver mutations and oligometastasis, SBRT is an effective and convenient option with relatively limited toxicity and could be considered as a treatment option.
7. SRS has shown promising results in patients with limited brain metastasis and should be considered over WBRT in elderly and frail patients were deemed appropriate on a case-by-case basis.
8. Integrating palliative therapy alongside anticancer therapies have shown to improve quality of life and OS and should be initiated as early as possible in the management of elderly.

Selection Criteria and Search Strategies

References were identified for this review paper from publications in PubMed. Search terms used were "geriatric," "elderly," "lung cancer," "NSCLC," "assessment tools," "driver mutation," "EGFR," "ALK," "ROS1," "radiotherapy," "Stereotactic radiotherapy," "immunotherapy," "chemotherapy," "platinum based chemotherapy," "anti-VEGF," "life expectancy," and their combinations. Articles, abstracts, and summaries were also identified by searching the authors' files and the reference lists of selected articles. References were selected based on their relevance to the current practice of geriatric oncology.

Conflict of Interest

None declared.

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