Review Article

How old is "too old" for translational research?

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Background: Targeted therapies are now widely used for lung cancer management. Numerous biomarkers are performed in these patients in the diagnosis phase and have consequences on patient's management. There are some changes during elderly which can influence the biology of cancer; particularly mitochondrial dysfunction and deregulation of nutrient sensing. Elderly patients are candidate to these biological assessments, like younger ones.

Methods: We review all the published papers based on Mesh carries with "elderly", "lung cancer", "targeted therapy".

Results: After description of biological modification during elderly, the use of targeted therapies in non-small cell lung cancer (NSCLC) is presented and discussed. Tyrosine kinase inhibitors (TKIs) and antiangiogenic molecules were depicted in selected or unselected population.

Conclusions: Targeted therapies can be used in older patients with lung cancer and are sometimes an optimal choice in this particular population.

Keywords: Lung cancer; elderly; Tyrosine kinase inhibitors (TKIs); antiangiogenic agents

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Introduction

It is first necessary to define what we mean by an "old" person. The age threshold depends on the country, being generally 65 years in English-speaking countries, and 75 years in Europe. The most commonly used threshold is 70 years.

Whatever the chosen age definition, most cases of lung cancer occur during the latter part of life, 50% of cases over 65 years, 30% after 75 years (1,2). It is therefore important to care for these patients in the best possible conditions.

Geriatric indexes (3-5) have been developed in recent years to evaluate these patients. At the same time, questions have arisen as to the use of targeted therapies in this population. Even if chemotherapy has proven effective (6), it is reserved for patients in good general condition and does not take into account all the dimensions of these patients' functional changes (metabolic, pharmacological) or their comorbidities (7).

This raises the question of whether we can apply to this population the same translational approach as that used for younger patients (personalized chemotherapy, targeted therapy).

Biological modifications

A recent review of the literature (8) showed that aging has nine major biological effects: genomic instability, altered telomeres, epigenetic changes (affecting histone deacetylase inhibitors), leading to chromosomal instability, loss of hemostasis, growth hormone (GH) dysregulation, mitochondrial dysfunction, cellular senescence, impaired cell-cell communication, and impaired stem cell activity in blood.

The most striking modifications affect the anterior pituitary, with a potential impact on insulin-like growth factor 1 (IGF-1). This pathway (*Figure 1*), which is the last to be affected by aging, impacts multiple activation pathways (PTEN, PI3K, FOXO, mTOR and ROS) which may also be involved in lung cancer.

One must therefore take into account not only the

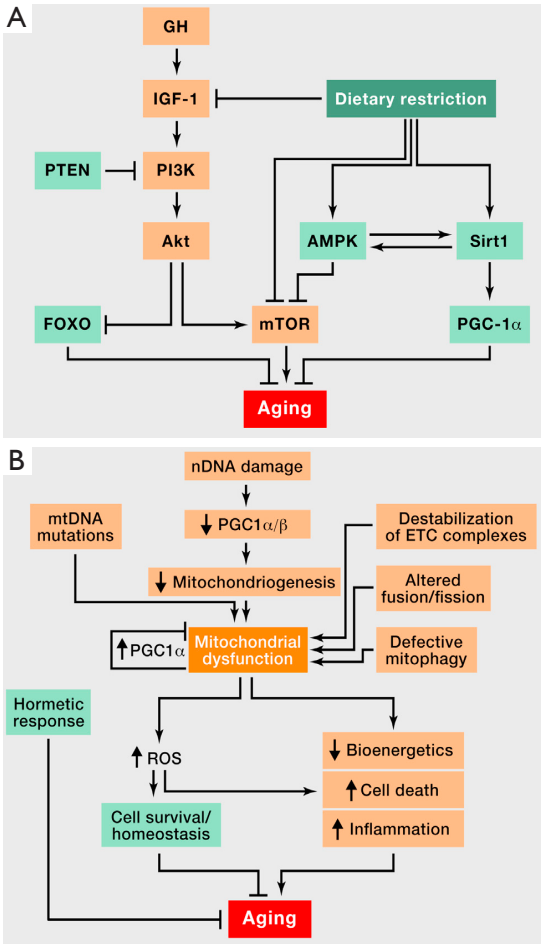

Figure 1 Physiological changes with aging (8). (A) Deregulated nutrient sensing. Overview of the somatroph axis involving growth hormone (GH) and the insulin/insulin growth factor 1 (IGF-1) signaling pathway and its relationship to dietary restriction and aging; (B) mitochondrial dysfunction.

physiological changes of aging but also factors also involved in the development of lung cancer. Further research is needed to identify links between biological aging and pathways involved in pulmonary carcinogenesis.

Targeted therapeutics in NSCLC

One of the main issues facing these patients is which treatment to choose first. Tyrosine kinase inhibitors (TKIs) have a recognized role, initially being assimilated to the "Lazarus syndrome" (9,10). The first trials in elderly patients involved gefitinib (*Table 1*). Gefitinib does not have more major adverse effects in this population than in younger patients.

Trials were subsequently conducted with erlotinib (17-20), including one devoted specifically to patients over 80 years of age (17). This trial, conducted in China, involved 203 patients, of whom 75 (32%) received first-line TKI therapy, while 46% received supportive care alone, and the remainder received chemotherapy. Two recents French trials have compared erlotinib first versus chemotherapy and the opposite sequence in fit (21) and unfit patients (22). Whatever could be the sequence, results were similar between the two groups.

However, epidermal growth factor receptor (EGF-R) mutated patients treated with TKIs were most benefited in terms of overall survival compared to EGF-R wild type patients. Survival was also better in EGF-R wild-type patients treated with erlotinib compared to those treated with chemotherapy.

There are no specific trials of angiogenesis inhibitors in elderly lung cancer patients.

Antiangiogenic agents are also widely used for lung cancer treatments.

In the ECOG 4599 trial (23), comparing carboplatin-paclitaxel to carboplatin-paclitaxel-bevacizumab. Bevacizumab did not improve survival in the subgroup of patients aged 70 years or more (median 74 years), although there was a trend towards a better response rate and longer progression-free survival in the bevacizumab group. Toxicity, and especially hematologic adverse effects, was higher in the bevacizumab arm. In the AVAIL study (24) of cisplatin-gemcitabine with or without bevacizumab, progression-free survival was significantly better with bevacizumab and was similar in the older and younger subgroups, without specific toxicity in the older group; however, the median age of patients over 65 was only 68 years. In the ARIES prospective cohort study (25) evaluating the use of bevacizumab in combination with first-line chemotherapy, progression free survival (PFS) was respectively 6.6 and 6.7 months in patients <70 years (n=1,320) and ≥70 years (n=647), and overall survival was respectively 14.2 and 12.2 months, i.e., largely inferior in patients ≥70 years. There was no excess toxicity in these latter patients.

The role of bevacizumab combined with platinum-based chemotherapy in patients ≥70 years of age needs to be prospectively evaluated in a phase III trial specifically dedicated to elderly patients.

Conclusions

There is thus no reason why elderly patients should not receive targeted therapies, provided that their general

Table 1 Main trials with gefitinib as first-line treatment in special patients populations (elderly or unfit) with advanced NSCLC d'après (11)

Author (Ref)	Trial				
	Inclusion criteria	Molecular selection (EGF-R mutation positive)	Number of patients	Median progression-free survival (m)	Median overall survival
Crino *et al*. (12)	Elderly (≥70 years)	No	97	2.7	5.9
Minegishi *et al*. (13)	Elderly (≥75 years)	Yes	31	13.6	Not reached
Asami *et al*. (14)	Elderly (≥75 years)	Yes	15	10.4	Not reached
Uruga *et al*. (15)	Elderly (≥70 years)	Yes	9	13	17.2
Goss *et al*. (16)	Unfit (WHO perfermance status 2 or 3)	No	100	1.4	3.7
Inoue *et al*. (9)	Unfit (20-74 years with ECOG PS 3-4, 75-79 years with PS 2-4, ≥80 years with PS1-4)	Yes	30	6.5	17.8

m, months; NSCLC, non-small cell lung cancer; ECOG, Eastern Cooperative Oncology Group.

condition and comorbidities are taken into account. In the future, it may be possible to identify the patient subgroups most likely to benefit from the treatment options like first-line targeted therapy, or a combination of targeted therapy with chemotherapeutic agents with proven activity in elderly patients. This may be better accomplished by biological profiling of the disease, which may be easier performed in liquid biopsies, like cfDNA or CTCs, as tissue acquisition through a rebiopsy is often difficult in "old" patients. Indeed, as Tsao *et al*. (26) showed in the BATTLE trial, elderly patients should not have to forego biological analyses. Screening for known genetic abnormalities (27,28) in this high-incidence population will lead to improved survival (28), in combination with clinical tools.

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