Lung Cancer 106 (2017) 50–57

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Review

SBRT for oligoprogressive oncogene addicted NSCLC

L. Basler*, S.G.C. Kroeze, M. Guckenberger

Department of Radiation Oncology, University Hospital Zurich, Rämistrasse 100, CH 8091 Zurich, Switzerland

ARTICLE INFO

Article history:
Received 9 December 2016
Accepted 5 February 2017

Keywords:
Stereotactic body radiotherapy (SBRT)
Oligoprogressive disease (OPD)
Oncogene addicted lung cancer
Resistance to targeted therapy
Tyrosine kinase inhibitors
EGFR mutation

ABSTRACT

Lung cancer is one of the leading causes of cancer death in men and women and treatment outcome continues to lag behind other common cancer types. A subset of lung adenocarcinoma patients exhibit a somatic mutation in EGFR or an ALK rearrangement. In these patients, targeted TKI therapy results in higher response rates, improved PFS and reduced side effects compared with platinum-based chemotherapy. Despite initial activity of the TKIs, ultimately all patients present with disease progression after about a year on TKI therapy due to resistance development. About 15–47% of patients present with limited oligoprogressive disease (OPD): such patients show only a limited number of metastases with progression in radiological imaging. Radical local treatment to all oligoprogressive lesions is thought to eradicate the de-differentiated clones and restore overall sensitivity of the metastatic disease. Retrospective studies suggest that aggressive local treatment using stereotactic body radiotherapy (SBRT), surgery or others can be used to eradicate TKI-resistant subpopulations enabling prolonged TKI treatment "beyond progression", which may lead to increased PFS and overall survival. This review focuses on the biological background of resistance development, systemic and local treatment options with a focus on SBRT, as well as challenges in defining the state of OPD and current clinical studies in oligoprogressive oncogene addicted NSCLC.

Contents

* Corresponding author.
E-mail address: Lucas.Basler@usz.ch (L. Basler).

http://dx.doi.org/10.1016/j.lungcan.2017.02.007
0169-5002/

1. Introduction

Lung cancer is one of the leading causes of cancer death in men and women. In 2012 lung cancer was diagnosed in 1.8 million people and resulted in 1.6 million cancer deaths world wide [1]. Non-small cell lung cancer (NSCLC) is the most common lung cancer type and accounts for 85% of patients while small cell lung cancer (SCLC) incidence has decreased over the past two decades [2]. Around two thirds of NSCLC patients present with inoperable Stage IV and one third already shows advanced metastatic disease at the time of diagnosis. The 5-year survival rate in the United States is 17% [3] and progress in improving the outcome has lagged behind other common cancer types for many decades.

2. Oncogene addicted NSCLC

2.1. Definition

In the past decade common somatic driver oncogene mutations were identified such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) as well as less common MET, ROS1, BRAF and other mutations. Their identification led to the development of targeted therapies using tyrosine kinase inhibitors (TKIs), which completely changed the systemic treatment of these subpopulations of patients with mutation positve, advanced NSCLC. Approximately 10–20% of Caucasian and 30–40% of Asian NSCLC adenocarcinoma patients exhibit a somatic mutation in EGFR, with an additional 4–7% of patients having an ALK rearrangement. The frequency is higher in never smokers, women and patients of East Asian ethnicity [4]. In these molecularly defined populations, targeted therapy using TKIs has produced higher response rates (RR), improved progression free survival (PFS), better tolerability with reduced side effects and superior quality of life (QoL) compared with standard platinum-based chemotherapy, which has been shown in several randomized trials [5].

2.2. Resistance to oncogene targeted therapies and second-line therapy

Despite initial activity of the TKIs, acquired resistance eventually develops with median PFS of 8–10 months in patients with ALK rearrangements and 9–13 months in patients with EGFR mutations and ultimately all patients develop progressive disease [6–10]. This acquired resistance can be attributed to a number of common mechanisms in the majority of cases, although reasons remain unknown in ~35% of cases [11–13]. A rebiopsy with molecular analysis should be performed in patients with acquired resistance to TKIs in order to identify the molecular mechanism of resistance. If it is not feasible to perform a rebiopsy a liquid biopsy represents a new method for tumor genotyping and should be considered at the time of progression [14].

2.2.1. EGFR drug target alterations

The most common acquired resistance against first generation TKIs involves the development of a second EGFR mutation, T790 M, which can be found in 49–60% of resistant patients and leads to a change in the ATP-binding pocket of EGFR with increased affinity for ATP and consecutive reduced affinity for reversible TKIs (e.g. erlotinib or gefitinib) by competitive inhibition or steric hindrance [15–18].

This discovery led to the development of third-generation TKIs, e.g. osimertinib, which bind to EGFR in an irreversible way and render the reduced affinity irrelevant. These new drugs represent the treatment of choice in these cases [19,20].

2.2.2. EGFR bypass track activation

Another way of developing a resistance against treatment with TKIs is the activation of bypass tracks. Examples for this are MET amplification (5%), HER2 amplification (8–13%), BRAF- (1%), EMT- (1–2%) and PIK3CA-singaling (1%), as well as transition to SCLC (10%) [13,18,21,22]. Multiple clinical trials investigating the inhibition of these bypass tracks are currently running with mixed results [23].

2.2.3. ALK drug target alterations

ALK amplification (6–16%) and several ALK mutations (22–33%) have been discovered. Compared to the common T790M mutation as mechanism of acquired resistance in EGFR mutated patients there appears to be no dominant additional ALK mutation, which renders targeting of these secondary mutations quite difficult [23]. Additionally the concentration of crizotinib in the cerebrospinal fluid is negligible [24] which limits its potential in patients with brain metastases.

Ceritinib is a second-generation TKI which, compared to crizotinib, offers a higher ALK selectivity and subsequently 20 times higher potency and increased CSF penetration but does not inhibit the MET kinase [25–27]. Two phase I studies were able to show a benefit of ceritinib in patients with crizotinib resistance with an ORR of 56% and PFS of 6.9 months [28]. In Japan the second generation ALK inhibitor alectinib is approved for all patients with advanced NSCLC and ALK-rearrangement and demonstrated superiority compared to crizotinib as a first-line treatment in a randomized phase III trial [29]. Other second-generation ALK inhibitors are in development mainly focusing on increased CSF penetration and broader activity against secondary ALK mutations [30].

2.2.4. ALK bypass track activation

Similar to acquired resistance in EGFR-mutated patients, bypass track activation is an important mechanism of resistance in ALK-rearranged patients with possible increase of EGFR signaling (30–35%), KIT amplification (10%) or other changes in driver mutations (5%) [18].

3. Oligoprogressive disease (OPD)

3.1. Definition

The concept of oligometastatic disease was first described in 1995 by Hellman and Weichselbaum as an intermediate state between a localized and systemic disease [31]. Agressive local treament to all oligo-metastatic lesions is considered as a curative apporach in this concept, which is supported by observations from irradiation and resection of lung and liver metastases: in patients with colorectal carcinoma or sarcoma [32–35] long-term overall survival is achieved in about 20–25% of the patients. Similar data on better-than-expected survival after local treatment of oligometastatic diease is available for NSCLC as well [36–38].