Cancer Treatment Reviews 41 (2015) 634–645

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Complications of Treatment

Safety of cranial radiotherapy concurrent with tyrosine kinase inhibitors in non-small cell lung cancer patients: A systematic review

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ARTICLE INFO

Article history:
Received 1 April 2015
Received in revised form 5 May 2015
Accepted 6 May 2015

Keywords:
Tyrosine kinase inhibitor
NSCLC
Cranial radiotherapy
Neurotoxicity
EGFR
ALK

ABSTRACT

Recently, non-small cell lung cancer (NSCLC) has been partly subclassified into molecularly-defined oncogene "addicted" tumors for which targeted agents are available. Tyrosine kinase inhibitors (TKI) are currently approved for patients with an activating epidermal growth factor receptor (*EGFR*) mutation or anaplastic lymphoma kinase (*ALK*) rearrangement. In these patients, brain metastases are often the first site of progression while on TKI treatment. The TKI may however still be active on extra-cranial sites and clinicians are thus faced with the question if the TKI may be continued during cranial radiotherapy. Advantages of combining TKI with cranial radiotherapy would be a possible synergistic effect on the brain metastases and the prevention of a systemic disease flare-up. A disadvantage is the possibly increased risk of (neuro)toxicity. The present systematic review addresses the toxicity of combining TKI with cranial radiotherapy in NSCLC patients.

Introduction

Increasingly, new molecular features of non-small cell lung cancer (NSCLC) are being discovered, leading to an unprecedented growth of targeted agents. These are often tyrosine kinase inhibitors (TKI) [1]. Currently, TKI are approved for metastasized NSCLC patients with an activating epidermal growth factor receptor (*EGFR*) mutation or an anaplastic lymphoma kinase (*ALK*) rearrangement, either as first line or beyond [2,3]. Examples are erlotinib, gefitinib, afatinib and icotinib (China only) for *EGFR*-mutations, and crizotinib and ceritinib (USA only) for *ALK*-rearrangements. Approximately 20–35% of these patients are diagnosed with brain metastasis at initial diagnosis and these patients are often amenable for initial treatment with TKI [4–8]. However, a substantial part will develop new brain metastasis or progression of brain metastasis during treatment. On erlotinib and gefitinib treatment 14–33% of patients develop (progression of) brain metastasis [9–15]. In patients with a survival beyond five years, this percentage increases to 52.9% [6]. On crizotinib treatment 70% of patients experience progression of brain metastases after an initial cerebral disease control rate of 60% (median time to intracranial progression: 7 months). 20% of patients without brain metastasis at initial NSCLC diagnosis develop brain metastasis during crizotinib treatment and this increases to about 58% in patients with a survival beyond three years [6,8]. In these patients, the brain is often the first and/or only site of progression (oligo-progression) [8,12,14,16].

The TKI may however still be active on extra-cranial sites and clinicians are thus faced with the question if the TKI may be continued during cranial radiotherapy. Although there are pre-clinical studies suggesting that TKIs enhance radiation effects, the effects on normal tissues are unclear [17–20]. Data show that some molecular features of the tumor are not only related to response to TKI but also to radiation susceptibility of the tumor. As an example, tumors with activating *EGFR*-mutations not only show a high probability to respond to EGFR–TKI but also to radiation [21]. In current guidelines (ESMO 2014, NCCN 2014, ASTRO 2012) no recommendations are made regarding the concurrent use of TKI's and cranial radiotherapy in NSCLC patients with an activating

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http://dx.doi.org/10.1016/j.ctrv.2015.05.005
0305-7372/

mutation [2,3,22,23]. Frequently, TKI's are discontinued during cranial radiation because of (neuro)toxicity concerns. However, toxicity (e.g., radiation pneumonitis) does not seem to increase when EGFR–TKI are combined with thoracic radiotherapy in the majority of studies although some did report a higher incidence of grade 3–5 radiation pneumonitis [24–27]. Advantages of combining TKI with cranial radiotherapy would be a possible synergistic effect on the brain metastases and the prevention of a systemic disease flare-up. The latter has been described in both *EGFR*-mutated patients (23% of patients, median time to disease flare-up 8 days, range 3–21 days) and in an *ALK*-translocated patient (time to disease flare-up 15 days) [28,29]. Among the factors associated with an increased risk for a disease flare-up was the presence of central nervous system (CNS) disease [28].

The aim of the present systematic review is to address the toxicity of combining TKI with cranial radiotherapy in NSCLC patients as, to the best of our knowledge, there is no systematic review on this topic. The focus will be on neurotoxicity. When possible, a daily practice advice will be formulated.

Methods

Search strategy and selection criteria

The literature search was performed following the PICO method [30] and is shown in Appendix 1. This search was used to identify studies in Pub Med, EMBASE, Web of Science and the Cochrane Library from 2001 until the search date in November 2014. Additionally, clinicaltrials.gov was searched to identify unpublished or ongoing clinical trials.

Selection criteria were established prior to the search and selection of articles. These included human only studies, including a minimum of 5 NSCLC patients treated with concurrent cranial radiotherapy and TKI's (*EGFR*: erlotinib, gefitinib, afatinib, icotinib, *ALK*: crizotinib, ceritinib and alectinib). As safety was the primary endpoint there was no restriction on the presence of a targetable mutation. Studies with whole brain radiotherapy (WBRT) as well as stereotactic radiosurgery/stereotactic radiotherapy (SRS/SRT) were included. Language was restricted to English, German and Dutch. Original articles and conference proceedings were included, reviews were excluded. Additionally, references of eligible articles were manually searched to find other relevant studies. All inclusion and exclusion criteria are summarized in Table 1.

Outcomes

One researcher (LH) conducted the search and selection of eligible studies. All articles were then evaluated by another independent reviewer (JS). When available, the following data were extracted from eligible studies by one researcher (LH) and independently by another researcher (JS): author, year of publication, original article or conference proceeding only, type of study, duration of study, number of included patients, *EGFR* mutation/*ALK*-translocation status available (yes/no) and results of mutation testing, dose cranial radiotherapy (WBRT and/or SRS/SRT), description of TKI used (including dosing and timing), safety and efficacy outcomes.

Data were extracted and tabulated independently (Appendix 2). Consensus was reached by discussion between reviewers when outcomes differed.

Table 1
Inclusion criteria for this review.

Subjects included	Human only
Language	English, German, Dutch
Article type	Original article, conference proceeding
Number of patients	⩾5
Site of primary tumor	NSCLC
Tumor stage	IV
Treatment	WBRT and/or SRS/SRT concurrent with TKI (EGFR– or ALK–TKI)
Follow up period	All
Outcome	Safety/adverse events one of the outcomes measured

Abbreviations: NSCLC: non-small cell lung cancer; WBRT: whole brain radiotherapy; SRS: stereotactic radiosurgery; SRT: stereotactic radiotherapy; TKI: tyrosine kinase inhibitor; EGFR: epidermal growth factor receptor; ALK: anaplastic lymphoma kinase.

Results

Search results

The initial search in the four databases included 710 articles in total. Using Endnote and manual screening, 179 duplicate articles were excluded. Another 461 articles were excluded based on not relevant titles for this study, 70 articles were further screened. After reading of the abstracts, another 43 articles were excluded based on the exclusion criteria. Of the 27 remaining articles and conference proceedings, the whole article was read (not possible for conference proceeding). Based on the exclusion criteria, 11 articles and 3 conference proceedings were eligible to include in this review. With a manual search of the reference list of the included articles one other relevant article was found (flowchart in Fig. 1).

Description and quality of the studies

Of the 12 original articles and 3 conference proceedings that matched the selection criteria and were included in this review, 6 evaluated erlotinib concurrent with WBRT (one study combined WBRT with SRS) [31–36], 4 evaluated gefitinib concurrent with WBRT [37–40] and in 3 studies both drugs were studied [41–43]. In 2 studies icotinib concurrent with WBRT was studied [44,45]. For afatinib, crizotinib, ceritinib and alectinib no studies were found concurrent with cranial radiotherapy.

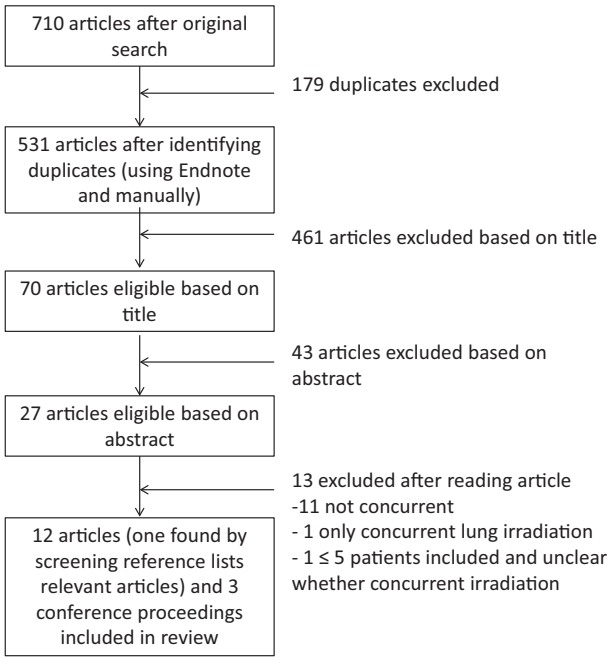

Fig. 1. Flowchart article selection.