Cancer Letters 321 (2012) 101–109

Contents lists available at SciVerse ScienceDirect

Cancer Letters

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

Mini-review

Antiangiogenic agents as second-line therapy for advanced non-small cell lung cancer

Karen L. Reckamp *

Department of Medical Oncology and Therapeutics Research, City of Hope and Beckman Research Institute, 1500 E. Duarte Rd., MOB 1001, Duarte, CA 91010, USA

ARTICLE INFO

Article history:
Received 25 November 2011
Received in revised form 19 January 2012
Accepted 28 January 2012

Keywords:
Angiogenesis
Non-small cell lung cancer
Tyrosine kinase inhibitor
Vascular disrupting agent
Second-line therapy

ABSTRACT

With the approval of the antiangiogenic antibody bevacizumab in non-small cell lung cancer (NSCLC) and other malignancies, the tumor vasculature has emerged as a worthwhile therapeutic target. Second-line therapies have the potential to improve overall survival and quality of life over best supportive care alone. Accordingly, phase II and phase III studies are actively evaluating antiangiogenic treatments in the second-line setting in NSCLC, and results are awaited. Such therapies include antiangiogenic antibodies, small molecule inhibitors, and vascular-disrupting agents. This review will present the current landscape of angiogenesis inhibition in NSCLC, focusing on use as second-line therapy.

© 2012 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Non-small cell lung cancer (NSCLC) accounts for more than 85% of all lung cancer cases, and an estimated 156,940 deaths from cancers of the lung and bronchus will occur in 2011 [1,2]. With lung cancer ranking as the leading cause of cancer-related deaths worldwide [2,3], further advances in all lines of therapy are urgently needed. NSCLC is often diagnosed at an advanced stage, for which systemic chemotherapy forms the therapeutic cornerstone [1]. Although the role of single-agent maintenance chemotherapy following first-line therapy in NSCLC has demonstrated improved outcomes, prolonging first-line doublet chemotherapy beyond 4–6 cycles does not provide additional meaningful benefit [4]. In addition, platinum-based doublet chemotherapy is associated with significant toxicity, including hematological events, nephrotoxicity, and gastrointestinal events [5].

At the time of progression following first-line treatment, patients considered fit for further therapeutic interventions may receive second-line therapy, which has the potential to improve clinical outcomes and quality of life over best supportive care [1,6,7]. In the second-line setting, combination chemotherapy is associated with a higher objective response rate (RR) and longer progression-free survival (PFS) relative to single-agent chemotherapy but generally leads to increased toxicity without prolonging overall survival (OS) [8]. Single-agent docetaxel (Taxotere®, Sanofi-Aventis; Bridgewater, NJ) had traditionally been the accepted second-line treatment for NSCLC [7], and more recently, pemetrexed (Alimta®, Eli Lilly and Company; Indianapolis, IN) and erlotinib (Tarceva®, Genentech; South San Francisco, CA), an epidermal growth factor receptor (EGFR) inhibitor, have also become available [1,9–12]. Despite these advances, improved therapies in the second-line setting are clearly needed.

The discovery of the role of angiogenesis in tumorigenesis and metastasis has paved the way for novel antiangiogenic therapies. First-line carboplatin/paclitaxel in combination with the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab (Avastin®, Genentech, Inc.; South San Francisco, CA) is a US Food and Drug Administration (FDA)-approved and clinical practice-guideline recommended option for patients with nonsquamous, unresectable, locally advanced, recurrent or metastatic NSCLC [1,13]. With the use of bevacizumab-containing first-line chemotherapy, bevacizumab should be continued until progression, a relatively new concept known as continuation maintenance (there are a number of other cytotoxic and biologic options for continuation or switch maintenance) [1]. In addition to VEGF, the most well known and extensively studied angiogenic growth factor [14–16], other proangiogenic factors (e.g., platelet-derived growth factor [PDGF], fibroblast growth factor [FGF]) have also been evaluated as therapeutic targets in NSCLC [17,18]. Synergistic interactions among these growth factor pathways have been described [19,20] and the PDGF and FGF pathways have been implicated in resistance to anti-VEGF therapy [21–23]. Whereas monoclonal antibodies and small molecule tyrosine kinase

* Tel.: +1 626 256 4673x63155; fax: +1 626 930 5461.
E-mail address: kreckamp@coh.org

0304-3835/$ - see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.canlet.2012.01.041

inhibitors (TKIs) directed against various angiogenic pathways are intended to prevent the formation of new vasculature, a new class of vascular-disrupting agents (VDAs) is being developed as an anti-angiogenic strategy for which endothelial cells and pericytes of existing vasculature are the therapeutic targets [24] (Fig. 1). Currently, a number of agents including bevacizumab, other antiangiogenic antibodies, small molecule inhibitors, and VDAs are being evaluated in the second-line setting in NSCLC.

2. Agents targeting angiogenic pathways

Investigational antiangiogenic antibodies, small molecule inhibitors, and VDAs that have been or are being actively evaluated in phase II and/or phase III clinical trials for the second-line treatment of advanced NSCLC are summarized in Table 1, with data from individual clinical trials discussed herein. Ongoing second-line NSCLC clinical trials of these agents for which results are awaited are summarized in Table 2.

2.1. Antibody-based therapies

2.1.1. Bevacizumab

Bevacizumab in combination with chemotherapy has established activity in the first-line setting in NSCLC, but may be associated with an increased risk of potentially serious toxicities. It is also important to recognize that the E4599 and AVAiL trials, as discussed below, were conducted in highly selected patient populations—patients with nonsquamous disease with a good performance status (0 or 1) and without clinically significant hemoptysis, central nervous system (CNS) metastases, or uncontrolled hypertension. In the E4599 phase III trial of carboplatin/paclitaxel with or without bevacizumab (15 mg/kg) in 878 patients with recurrent or advanced nonsquamous NSCLC, bevacizumab significantly prolonged the primary endpoint, OS (median 12.3 vs 10.3 months; hazard ratio [HR], 0.79; 95% confidence interval [CI], 0.67–0.92; $P = 0.003$) [13]. Bevacizumab was also associated with improved RR (35% vs 15%; $P < 0.001$) and PFS (median 6.2 vs 4.5 months; HR, 0.66; 95% CI, 0.57–0.77; $P < 0.001$). However, 15

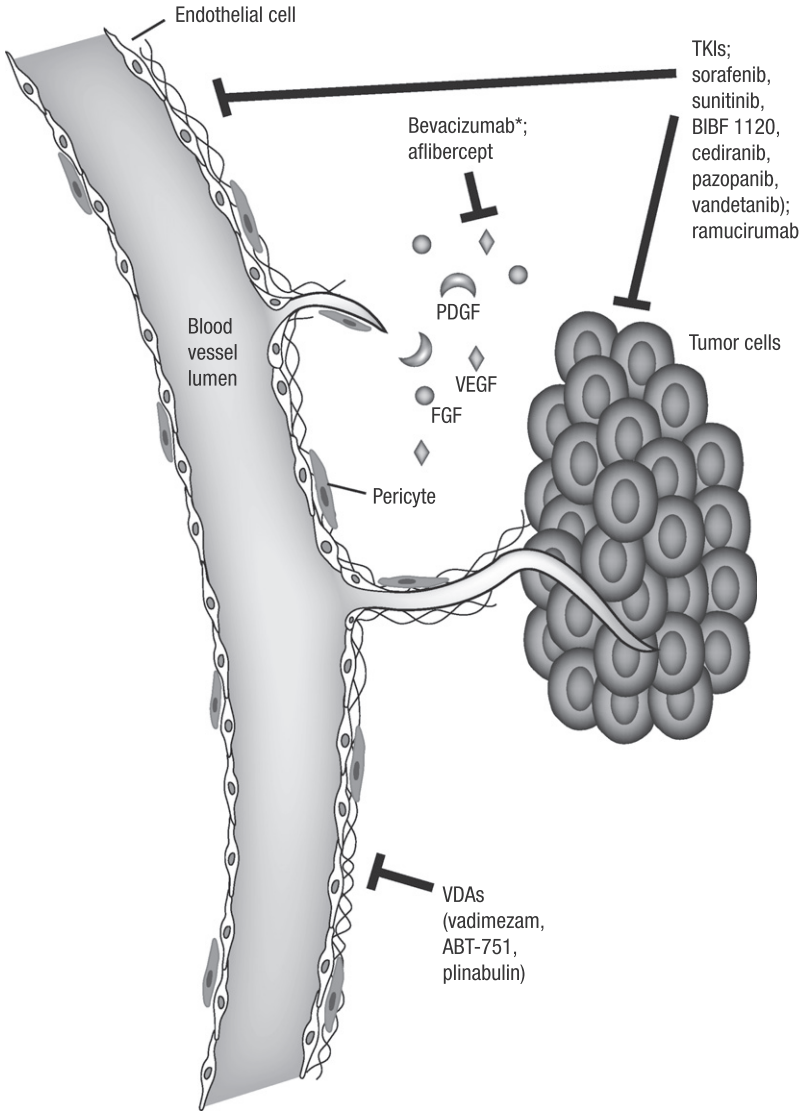

Fig. 1. Targets of investigational antiangiogenic agents. Mechanism of action of antiangiogenic monoclonal antibodies, antiangiogenic TKIs, and vascular disrupting agents. Approved for use by the US FDA. Adapted from Nguewa et al. [70]. Copyright © 2011, Informa Healthcare. Reproduced with permission of Informa Healthcare. FDA, Food and Drug Administration; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; TKI, tyrosine kinase inhibitor; US, United States; VDA, vascular-disrupting agents; VEGF, vascular endothelial growth factor.

Download English Version:

https://daneshyari.com/en/article/2113258

Download Persian Version:

https://daneshyari.com/article/2113258

Daneshyari.com