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Review

Farletuzumab in lung cancer

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ABSTRACT

Folate is essential for proliferating cells and folate transport pathways and folate-dependent metabolic processes show promise as targets for anti-neoplastic therapy. Folate receptor α (FOLR1), a folate transporter, is an attractive target for anti-neoplastic therapy due to its high affinity for folate, restricted range of expression in normal tissue and differential over-expression in malignant tissue. FOLR1 is expressed in non-small cell lung cancer, with a higher expression in adenocarcinoma compared with squamous cell carcinoma. Farletuzumab is a monoclonal antibody targeting FOLR1 which in pre-clinical studies led to cytotoxicity of FOLR1-expressing cells, inhibited tumor growth in animal models and showed limited reactivity with normal tissue. In phase I/II trials, farletuzumab was well tolerated as a single-agent and in combination, without additive toxicity with chemotherapy. An ongoing phase II, double blind, placebo-controlled study is evaluating farletuzumab in patients with FOLR1 expressing metastatic adenocarcinoma of lung.

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1. Introduction

Lung cancer is the leading cause of cancer death both men and women worldwide [1,2]. Non-small-cell lung cancer (NSCLC) constitutes approximately 85% of lung cancers. About 40% of patients with newly diagnosed NSCLC have metastatic disease at presentation [1]. In these patients, as well as those who relapse after initial definitive therapy, platinum-based systemic chemotherapy is known to improve survival, quality of life and symptom control compared with supportive care in patients with advanced NSCLC [3]. However, the median overall survival is only about a year, only 3.5% of patients survive 5 years after diagnosis and chemotherapy is associated with high morbidity [4,5]. In recent years, targeted therapies against specific molecular alterations in patients have shown to improve outcomes over chemotherapy alone [6]. However, such targetable alterations have been detected in less than half of all NSCLC patients [7]. There is an unmet need for effective, yet minimally toxic therapies in advanced NSCLC.

Since folate is essential for proliferating cells, folate transport pathways and folate-dependent metabolic processes are attractive targets for anti-neoplastic therapy. Targeting folate-dependent enzymes have been successful in several malignancies. In NSCLC, pemetrexed, an approved agent for selected patients, is transported into cells by membrane folate carriers and targets folate-dependent enzymes involved in de novo biosynthesis of thymidine and purine nucleotides [8].

Cellular uptake of folate into cells is regulated by folate receptor α (FOLR1) and reduced folate carrier-1 (RFC1) [9]. RFC1 is more ubiquitously expressed in normal cells, binds folate at low affinity, and represents the sole folate uptake pathway for most normal cells [9]. In contrast, FOLR1 expression in normal tissue is limited largely to luminal surface of epithelial cells which do not have a supply of circulating folate [10]. In these cells, for example the epithelia of choroid plexus, proximal kidney tubules, type I and II pneumocytes in lung and trophoblasts in placenta, FOLR1 binds with high affinity and transports the circulating form of folate, N-5-methyltetrahydrofolate via endocytosis into the cytoplasm. Even among FOLR1 expressing tissues, the physiologic importance of the receptor as a folate transporter is apparent only in certain instances, for example, when there is limited availability of folate [10]. FOLR1 is differentially over-expressed in many malignant epithelial tumors including NSCLC [11–14].

The high affinity of FOLR1 for folic acid, an essential vitamin required in substantial quantities by virtually all cells, its restricted range of expression in normal tissue, differential over-expression in malignant tissue and discovery of ways to non-destructively introduce proteins utilizing the FOLR1-mediated endocytosis of folic acid have led to its evaluation as a potential target for therapy in FOLR1-expressing tumors [15,16]. Two primary approaches have been explored for targeting FOLR1: targeted drug delivery via

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folate-conjugated therapeutic compounds [17] and direct targeting and tumor cell death via humanized anti-FOLR1 monoclonal antibodies [18]. In this review, we discuss the rationale for use, preclinical data and ongoing studies of farletuzumab, a monoclonal antibody which targets FOLR1, emphasizing its potential role in treatment of NSCLC.

2. Folate receptor α expression in NSCLC

Among NSCLC, there is a differential expression of FOLR1 based on histology. Several studies have demonstrated higher levels of FOLR1 expression in adenocarcinoma histology than squamous cell carcinoma (SCC) [14,19–21]. In the largest of these studies, immunohistochemical (IHC) analyses of 320 surgically resected NSCLC specimens comprising of 202 adenocarcinomas and 118 SCCs demonstrated higher FOLR1 expression in adenocarcinoma than in SCC [19]. The mean expression scores were significantly higher in adenocarcinomas than in SCCs at membrane (72.2 vs. 11.3; $P < 0.001$) and cytoplasmic (91.6 vs. 35.9; $P < 0.001$) localizations. The correlation between FOLR1 expression and histology held true in a multivariate analysis, after adjustments for tumor histology, smoking history, sex, and disease stage: adenocarcinoma was more likely than SCC to express cytoplasmic (odds ratio [*OR*] = 4.39; $P < 0.0001$) and membrane (*OR* = 5.34; $P < 0.0001$) FOLR1 [19]. Using a small number of specimens, this study also detected a similar trend advanced NSCLC [19]. Gene expression profiling studies have also confirmed the relative abundance of expression of FOLR1 in lung adenocarcinoma [22–24]. The association of FOLR1 expression with alterations in other molecular pathways of known therapeutic relevance in NSCLC [e.g. epidermal growth factor receptor (EGFR) mutation, anaplastic lymphoma kinase (ALK) translocation) is not well established. Based on available data, surgically resected *EGFR* mutant tumors demonstrate higher expression of FOLR1 compared with EGFR wild type tumors [19,20].

In contrast from observations in other epithelial tumors [25–27], higher FOLR1 expression is associated with a better prognosis in early stage-NSCLC [20,21]. In adenocarcinoma patients who underwent surgical resection ($N = 55$), higher FOLR1 expression by IHC was associated with improved survival (HR 0.39, 95% confidence interval [*CI*] 0.18–0.85) [21]. Higher FOLR1 expression remained significantly associated with overall survival after adjusting for stage, age, gender, and race [21]. In a Japanese study of surgically resected NSCLC cases ($N = 119$), patients with higher FOLR1 expression had better 3-year survival rates (94.7% vs. 80.9%; $P = 0.008$) and disease-free survival (75.4% vs. 60.8%; $P = 0.038$) compared with patients who had lower FOLR1 expression [20]. There are limited data on the association between FOLR1 expression and prognosis in advanced NSCLC.

Although FOLR1 is expressed in normal lung, it is thought to be restricted to apical surfaces of polarized epithelial cells (i.e., the side facing the lumen), and not exposed to the blood stream and thus inaccessible to folate and folate conjugates [11,28].

3. Farletuzumab

Farletuzumab (MORAb-003) is a humanized monoclonal antibody of immunoglobulin G subtype 1 kappa (IgG1/κ) that targets FOLR1. It was derived by optimizing a FOLR1-binding murine antibody (LK26) using a whole cell genetic evolution platform [29,30]. Development of humanized version of LK6 was abandoned in the past due to its low affinity of 0.2 μM. After the optimization process, farletuzumab exhibited an affinity similar to the original murine LK26 antibody (approximately 2 nM) and a tissue binding profile consistent with the distribution of the folate receptor [31]. Rather than blocking FOLR1 mediated folate transport, farletuzumab is thought to result in tumor cytotoxicity due to antibody dependent cellular cytotoxicity, complement mediated cytotoxicity and inhibition of association of FOLR1and lyn kinase (Fig. 1) [31,32].

In vitro, farletuzumab inhibited FOLR1-dependent cell growth in Chinese hamster ovary (CHO) cells expressing FOLR1 [31]. In vivo, farletuzumab reduced tumor growth of human tumor xenografts in nude mice. In non-human primates, there were no observable toxicities and serum levels were dose linear. IHC in human and primate tissues showed identical binding and very limited reactivity of farletuzumab with normal tissue. The high affinity of farletuzumab

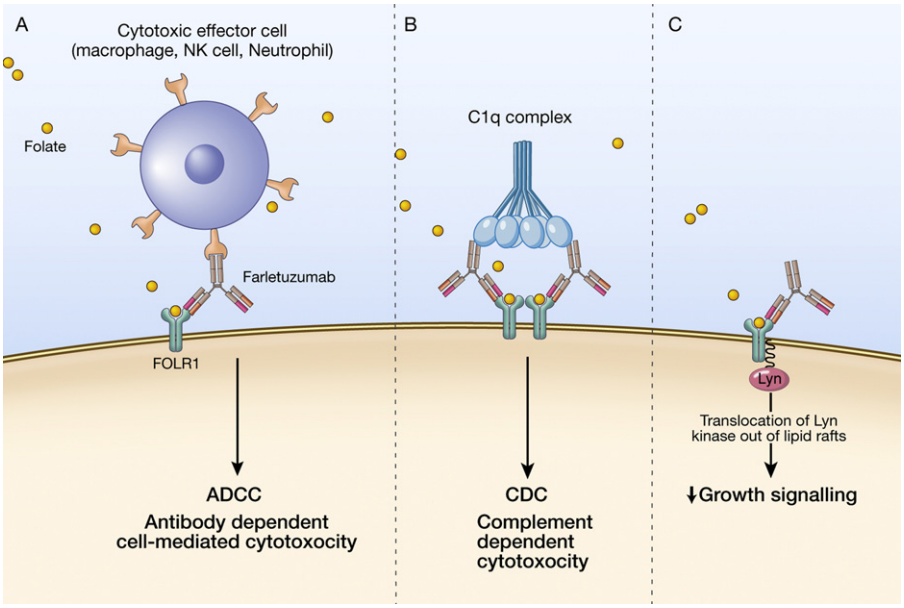

Fig. 1. Illustration of mechanisms of action of farletuzumab. Farletuzumab does not block FOLR1 mediated folate transport. Binding of farletuzumab to tumor cell recruits immune effector cells (e.g. granulocytes, natural killer cells, monocytes and macrophages) that kill the tumor cell via phagocytosis or cell lysis, a process known as antibody-dependent cellular cytotoxicity (ADCC) (A). It also activates the complement system that combines to form a membrane attack complex (MAC) resulting in complement-dependent cytotoxicity (CDC) (B). Farletuzumab may also disrupt the clustering of FOLR1 in the lipid rafts of cell membrane, thus disrupting the intracellular signaling by Lyn kinase and other proteins (C). Abbreviations: FOLR1, folate receptor α.