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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.

Keywords

adenocarcinoma; farletuzumab; folate receptor α ; monoclonal antibody; non-small cell lung cancer; immunohistochemistry

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

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Conflicts of interest

Anish Thomas and Raffit Hassan have no conflicts of interest. Julia Maltzman is an employee of Morphotek Inc.

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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 tissue, 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 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, pre-clinical 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 μ M. 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 FOLR1 and lyn kinase (Figure 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 for FOLR1 and its uptake by tumor were demonstrated in biodistribution studies of radiolabeled farletuzumab [33].

4. Phase I clinical trials

In a phase I dose escalation study, 25 heavily pretreated patients with platinum-refractory or resistant epithelial ovarian cancer received farletuzumab (12.5–400 mg/m²) on days 1, 8, 15, and 22 of a 5-week cycle [18]. Due to the high frequency of FOLR1 expression in epithelial ovarian cancer (approximately 90%), patients were not selected for tumor-FOLR1 expression. No dose limiting toxicities (DLT) (grade 3 treatment-related adverse event) were encountered and maximum tolerated dose (MTD) was not established as dose escalation continued to the maximum planned dose [18].

Rare samples exhibited human anti-human antibodies, but these did not correlate with adverse events or alterations in pharmacokinetic profile. IHC showed moderate cross-

reactivity of farletuzumab with lung and kidney; however, no clinically significant toxicities relating to these organs were observed. Pharmacokinetic parameters increased in an approximately dose-proportional manner. There were no objective responses. Since MTD could not be determined, the study recommended a phase II dose range of 2.5 to 10 mg/kg similar to standard dosing recommendations of other monoclonal antibodies [18]. The $C_{\max}$ (peak serum concentration) and AUC_{0-24} (area under the serum concentration-time curve) increased in an approximately dose-proportional manner. A similar pharmacokinetic profile was observed in a phase I study in Japanese patients [34].

Combination of farletuzumab (2.5mg/kg) with liposomal doxorubicin (30 mg/m²) and carboplatin [area under the curve (AUC) 4–5] administered every 4 weeks for 6 cycles, followed weekly farletuzumab maintenance, was well tolerated in a phase I study of women with platinum-sensitive epithelial ovarian cancer in first or second relapse [35].

5. Phase II clinical trials

In a phase II study, farletuzumab was evaluated as a single-agent and in combination with carboplatin (AUC 5–6) and taxane in 54 patients with platinum-sensitive epithelial ovarian cancer in first relapse [36]. Patients with low-volume or asymptomatic disease received single-agent farletuzumab (N=28) until disease progression, whereupon they could cross-over to receive combination therapy. Those with symptomatic or large-volume disease received farletuzumab with chemotherapy (N=26) every 3 weeks for 6 cycles followed by farletuzumab maintenance. Primary endpoints were normalization of CA125 and objective response rate (ORR). Twenty one patients who were receiving single agent farletuzumab crossed over to receive combination therapy at progression [36]. Farletuzumab was well-tolerated as a single-agent and in combination, without additive toxicity with chemotherapy. Of the 44 evaluable patients who received the combination, 89% had normalization of CA125 and in 21%; the second remission was equal to or longer than the first remission. Compared to historic data, high response rates were observed in patients with a first progression-free interval of <12 months (64% ORR). Single-agent farletuzumab did not result in objective responses [36]. An ongoing phase III trial is evaluating farletuzumab in patients with platinum-sensitive ovarian cancer at first relapse (NCT00849667).

6. Safety and tolerability

Clinical results from the phase I study suggested that single-agent farletuzumab is well tolerated [18]. Twenty patients (80%) experienced a total of 47 adverse events that were considered related to administration of study treatment. Twenty-three patients (92%) reported 53 adverse events of interest, defined as those adverse events, which reflect immunologic symptoms related to administration of a monoclonal antibody. The majority of adverse events were National Cancer Institute Common Terminology Criteria for Adverse Events grade 1 (mild) in severity, and there were no drug-related adverse events of grades 3, 4, or 5 (severe). There were no apparent dose-related trends in adverse event frequency or severity. The most common treatment-related adverse events were hypersensitivity reactions (15 patients; 60%), fatigue (12 patients; 48%), and diarrhea (4 patients; 16%). Hypersensitivity reactions, mostly fever and chills, were mild (grade, 1 or 2) and rapidly resolved with antipyretics and/or antihistamines [18]. In the phase II study farletuzumab was well-tolerated as a single-agent and in combination, without additive toxicity with chemotherapy [36].

7. Ongoing studies in NSCLC

Ongoing evaluation of farletuzumab in NSCLC is based on pre-clinical data from other epithelial tumors and its safety profile in combination with carboplatin/taxane doublet. A

phase II, multi-center, double blind, placebo-controlled study (NCT01218516), is evaluating farletuzumab in patients with FOLR1 expressing metastatic adenocarcinoma of lung. Barring other known reliable measures, FOLR1 expression is assessed using IHC of formalin-fixed, paraffin-embedded samples with a mouse anti-human folate receptor monoclonal antibody which specifically recognizes FOLR1. Eligible patients have tumors with 1+ or greater membranous staining in 5% of tumor cells (Biocare Medical, Concord, CA). With an estimated sample size of 120 patients, this study targets a 3-month improvement in PFS with the addition of farletuzumab to front-line platinum-based chemotherapy. Patients will be randomized in a 1:1 ratio to receive farletuzumab or placebo with six cycles of one of three platinum based chemotherapy combinations: carboplatin and paclitaxel, carboplatin and pemetrexed, or cisplatin and pemetrexed. After pre-medication with acetaminophen, farletuzumab (7.5 mg/kg) or placebo will be administered intravenously on weeks 1 and 2 of cycle 1 (loading dose) followed by once in 3 weeks from cycles 2 to 6 (induction therapy). Patients who experience clinical benefit from induction therapy will receive maintenance farletuzumab or placebo every 3 weeks until disease progression. Exploratory studies will evaluate the correlation between tissue IHC FOLR1 and serum and urine FOLR1 and their role as surrogate markers for response and survival. Results are expected in early 2013.

8. Conclusion

Since folate is essential for proliferating cells, folate transport and metabolism are attractive targets for anti-neoplastic therapy. The restricted expression of FOLR1 in normal lung and its differential over-expression in NSCLC has led to its evaluation as a potential target for therapy in NSCLC. Although lung adenocarcinoma is known to have a higher FOLR1 expression compared with squamous cell carcinoma, the association of FOLR1 expression with other molecular alterations of therapeutic interest is less clear. Unlike other epithelial malignancies, FOLR1 expression is associated with a better prognosis in early-stage NSCLC. Farletuzumab, a monoclonal antibody that targets FOLR1, led to cytotoxicity of FOLR1-expressing cells, inhibited tumor growth in animal models and showed limited reactivity with normal tissue in preclinical studies. 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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Figure 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 combine 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 .