Spotlight on Clinical Response

Molecular Cancer Therapeutics

Early FDG/PET Scanning as a Pharmacodynamic Marker of Anti-EGFR Antibody Activity in Colorectal Cancer

Geoffrey W. Krystal[1], Erin Alesi[1], and James L. Tatum[2]

Abstract

Panitumumab is an anti-EGF receptor (EGFR) antibody approved for use in treatment of chemotherapy-refractory colorectal cancers lacking K-RAS mutations. Despite overall response rates approximating 10%, no marker predictive of clinical benefit has been identified. We describe a chemotherapy-refractory patient whose clinical condition necessitated rapid identification of an effective agent in whom we used ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET)/computed tomographic scanning 48 hours after an initial dose of panitumumab to document a pharmacodynamic response to the antibody. The initial 46% ± 2.7% drop in SUV_{max} of four target lesions correlated with a partial response by Response Evaluation Criteria in Solid Tumors and a >90% drop in serum carcinoembryonic antigen at 8 weeks, indicating that an early decrease in FDG uptake may predict subsequent clinical benefit in response to anti-EGFR antibody therapy in colorectal cancer. *Mol Cancer Ther; 11(7); 1385–8. ©2012 AACR.*

Introduction

Panitumumab and cetuximab are monoclonal anti-EGF receptor (EGFR) antibodies approved for use in chemotherapy-refractory colorectal cancer (CRC). Single agent overall response rates are 9% to 12% and no clinically useful positive predictors of response have been identified as yet, although tumors with K-RAS mutations are unlikely to respond (1). Studies of patients with absent or low tumor EGFR expression by immunohistochemistry have found that response rates are statistically indistinguishable from those patients with higher EGFR expression, indicating that immunohistochemical staining may not always detect physiologically relevant receptor expression (2, 3). An important consequence of EGFR activation is increased glucose uptake and retention, which supports tumor energetic and biosynthetic requirements (4, 5, 6), suggesting that ^{18}F-fluorodeoxyglucose-positron emission tomography (FDG-PET) may be a sensitive assay for detection of changes in EGFR activity (7, 8). Here, we describe a chemotherapy-refractory patient whose tumor was negative for EGFR expression by immunohistochemistry in whom we used FDG-PET to show a panitumumab-mediated decrease in FDG accumulation over a period of 48 hours, leading to a progressive decline in metabolic activity and partial response by Response Evaluation Criteria in Solid Tumors (RECIST; ref. 9) criteria.

Authors' Affiliations: [1]Hematology/Oncology and [2]Radiology and Nuclear Medicine Services, Richmond Veterans Affairs Medical Center and the Massey Cancer Center, Virginia Commonwealth University, Richmond, Virginia

Corresponding Author: Geoffrey W. Krystal, Richmond Veterans Affairs Medical Center 111K, Hematology/Oncology Section, Virginia Commonwealth University, 1201 Broad Rock Blvd, Richmond, VA 23249. Phone: 804-675-5446; Fax: 804-675-5447; E-mail: gkrystal@vcu.edu

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Case report

The patient is a 31-year-old female referred for adjuvant chemotherapy following laparoscopic resection of a T3N2MO stage IIIC sigmoid adenocarcinoma. She had no family history of CRC, no other neoplastic lesions on colonoscopy, and genetic analyses were inconsistent with hereditary nonpolyposis CRC. Six months of adjuvant FOLFOX chemotherapy was administered and follow-up FDG-PET/computed tomography (CT) was negative.

Four months later she presented with abdominal pain and CT revealed a 14-cm complex right ovarian mass with 3 hepatic lesions. The patient underwent laparotomy with hysterectomy and bilateral salpingo-oophorectomy revealing metastatic colon cancer. Nine cycles of FOLFIRI chemotherapy with bevacizumab were administered, with abdominal CT and FDG-PET/CT showing partial responses of all hepatic lesions without evidence of other disease. The patient was taken to laparotomy for radiofrequency ablation however multiple small peritoneal implants were noted. The largest central metastasis was left as measurable disease but the 2 superficial hepatic metastases were ablated following biopsy. The biopsy was negative for K-RAS mutation and for EGFR expression (immunohistochemistry) by 2 independent laboratories. The patient was then treated with 6 cycles of single-agent irinotecan with bevacizumab and filgrastim on an every 3-week schedule, with stability of the central hepatic lesion on serial CT scans, after which she declined further therapy.

Nine weeks later she presented with symptomatic and radiologic evidence of bowel obstruction. A FDG-PET/CT

revealed multiple peritoneal and mesenteric metastases, multiple new liver metastases, and a left supraclavicular lymph node metastasis. She underwent laparotomy with bypass of obstructing lesions in the pelvis and presented to the medical oncology clinic for further therapy 4 weeks later. Given evidence that patients with EGFR immunohistochemical-negative tumors can respond to anti-EGFR antibodies (2, 3), it was decided to proceed with panitumumab treatment. However, to avoid continuation of ineffective therapy, we attempted to determine whether physiologically relevant levels of EGFR, undetectable by immunohistochemistry, were targeted by the antibody using early FDG-PET scanning.

Materials and Methods

Treatment and evaluation

Panitumumab (Amgen) was administered i.v. at a dose of 6 mg/kg every 2 weeks with carcinoembryonic antigen (CEA) determination before each treatment. PET imaging was conducted with integrated CT on a Phillips Gemini large bore TOF PET/CT 90 minutes following injection of 10 to 12 mCi of FDG (Cardinal Health). Scanning was carried out craniocaudal at 1.75 minutes per bed position, FOV 576 mm in 144 $\times$ 144 matrix in 3-D TOF mode generating 4-mm slices. For each study the subject had been fasting greater than 6 hours and blood glucose determinations were below 120 mg/dL at the time of FDG administration. FDG-PET/CT scans were obtained immediately before the first dose, 48 hours later, and immediately before the fifth dose of therapy.

Imaging analysis

Four target lesions were identified on the baseline PET/CT scan based on the ability to accurately measure them on the noncontrast CT portion of the study. These were a left supraclavicular node, 2 hepatic lesions and a preaortic lymph node. Volume of interest to encompass the entire lesion was defined on the baseline image and reproduced on subsequent scans. SUV_{max} and longest diameter were determined at sequential time points and percentage of reduction was calculated for each lesion.

Results

FDG-PET imaging showed a mean 46% $\pm$ 2.7% drop in the SUV_{max} of the 4 target lesions over 48 hours following the initial panitumumab dose, without meaningful change in size (Fig. 1; Table 1). Following the completion of 8 weeks of treatment, the mean SUV_{max} of the target lesions dropped by 74.4% $\pm$ 8.4%, which correlated with a 47.5% decrease in the sum of the longest diameters, consistent with a partial response by RECIST criteria. This response also correlated with a decline in CEA from122 ng/mL before treatment to 11 ng/mL after 8 weeks of treatment (Fig. 2).

Discussion

Both the chimeric anti-EGFR monoclonal antibody cetuximab and the fully human monoclonal panitumumab have been approved for the treatment of chemotherapy-refractory CRC. By binding to EGFR in the inactive state, these antibodies inhibit activation of intracellular signaling, including the RAS-RAF-MAPK and phosphoinositide 3-kinase (PI3K)-Akt pathways that play critical roles in regulating growth, apoptosis, and cellular glucose transport and retention (6, 10, 11). Retrospective analyses have showed that the 40% of patients with K-RAS mutations are unlikely to respond but no clinically applicable biomarkers predictive of benefit have been identified despite 10% overall response rates, which are only modestly improved to 17% in the K-RAS wild-type population (1, 12). Thus therapeutic trials lasting 6 to 12 weeks are required to identify the minority of patients with wild-type K-RAS who will derive clinical benefit. For the majority of patients who do not benefit, these therapeutic trials can delay the start of alternative therapies including clinical trials of investigational agents and come at great expense, given the high price of these biologic agents.

In the case described here, rapid identification of a potentially effective therapy was necessitated by the patient's progressive clinical deterioration from her

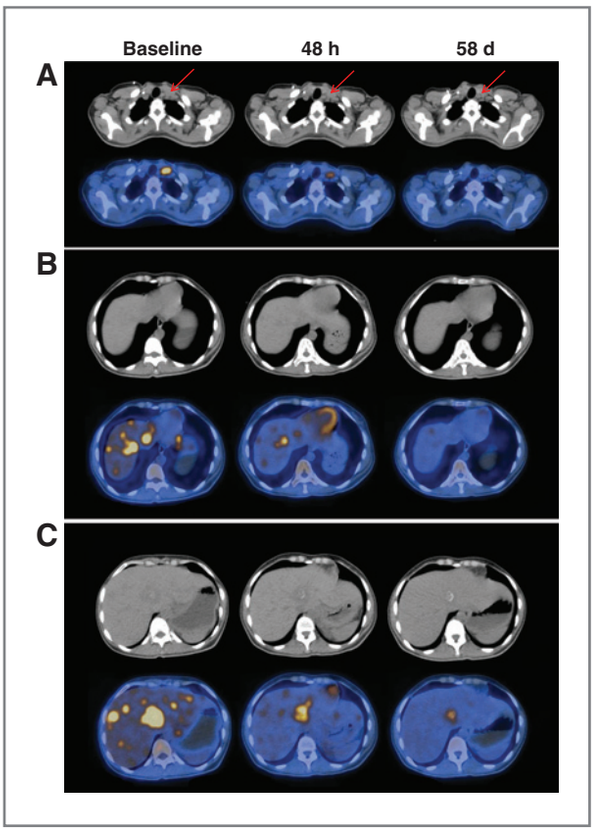

Figure 1. Representative noncontrast CT and fused FDG-PET/CT cuts. A, upper thorax illustrating the enlarged left supraclavicular node (arrow). B, superior right hepatic lobe illustrating multiple liver metastases with progressively decreasing FDG uptake. C, mid-liver illustrating the large central hepatic lesion. Note the increased calcification after 8 weeks of therapy.

Table 1. Change in FDG uptake and size of target lesions following panitumumab therapy

Target lesions	Baseline	Day 2	Day 58	D2 decrease	D58 decrease
L supraclavicular node					
SUV_{max}	7.1	3.9	2	45.07%	71.83%
Diameter,[a] mm	20.3	21.1	10.5	−3.94%	48.28%
R hepatic lobe					
SUV_{max}	12.9	6.6	1.8	48.84%	86.05%
Diameter,[a] mm	26.5	25.5	13.6	3.77%	48.68%
Central hepatic					
SUV_{max}	12.1	6.9	4.1	42.98%	66.12%
Diameter,[a] mm	45.0	40.4	24.6	10.22%	45.33%
Preaortic node					
SUV_{max}	7.9	4.1	2.1	48.10%	73.42%
Diameter,[a] mm	19.4	20.1	9.7	−3.61%	50.00%

[a]Longest diameter.

abdominal tumor burden. Given her prior therapies, panitumumab seemed the agent with the best therapeutic index despite her tumor being negative for EGFR expression by immunohistochemistry. While it might be expected that tumors lacking EGFR expression would not respond to this highly specific agent, tumors that express EGFR below the limit of detectability of the immunohistochemical assay might. Knowing that this patient's tumor was FDG-avid, we reasoned that acute changes in FDG uptake by PET could indicate modulation of EGFR function. Preclinical studies using lung and breast cancer cell lines showed marked inhibition of glucose uptake and retention over a period of hours following treatment with the kinase inhibitor gefitinib (7) and cetuximab (8), respectively. In addition, small clinical studies of gefitinib treatment of lung adenocarcinomas enriched for activating EGFR mutations have showed significant decreases in FDG uptake by PET after 2 days (13, 14). On the basis of these studies and those of radiolabeled panitumumab pharmacokinetics (J.L. Tatum, unpublished data) we chose a 48-hour time point to reassess FDG uptake by PET/CT.

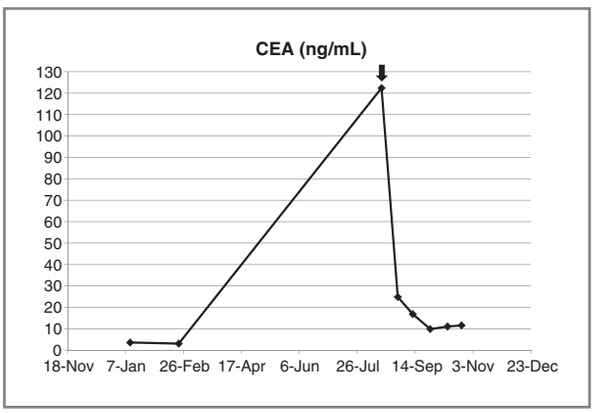

Figure 2. Progressive decline in CEA after initiation of panitumumab (arrow). Institutional normal value 0 to 5 ng/mL.

At 48 hours after the initial panitumumab treatment we noted uniform nearly 50% declines in target lesion FDG uptake (Table 1). This correlated well with a progressive decline in CEA (Fig. 2) and subsequent tumor shrinkage consistent with partial response by RECIST criteria at 8 weeks, with grade II acneiform rash as the only adverse event. This case shows the feasibility of using FDG/PET scanning as an early downstream pharmacodynamic marker of anti-EGFR monoclonal antibody activity. While FDG-PET has been routinely used to assess response in clinical trials and increasingly in clinical practice, when used to evaluate the efficacy of nontargeted cytotoxic therapy a sufficient time interval must be allowed for the acute tumor adaptive and host immunologic responses to subside, as well as a modest reduction in viable cell mass to occur, for interpretable results (15). However, when used to assess activity of agents targeting receptor tyrosine kinases regulating glucose metabolism, such as imatinib for gastrointestinal stromal tumors and gefitinib for lung adenocarcinomas, early changes in FDG uptake can be predictive of clinical response (14, 16). In these tumors, activating mutations in KIT and EGFR, respectively, are potent predictors of clinical response but in CRC such positive predictors of response to anti-EGFR antibodies do not exist. Use of FDG-PET in this setting may be a particularly sensitive assay owing to the ability of these antibodies to not only disrupt downstream signaling affecting glucose metabolism but also to potentially disrupt EGFR-mediated stabilization of the sodium/glucose cotransporter-1 (5).

While this case illustrates the feasibility of using early FDG-PET to show a pharmacodynamic response to anti-EGFR antibodies, which correlated with a clear partial response, this correlation may not always hold. The flexibility of tumors to use alternative receptors to activate downstream signaling pathways regulating glucose

metabolism has been well-established (17, 18, 19), so that some tumors may only experience a transient inconvenience following inhibition of EGFR, and those patients may not experience clinical benefit despite an early pharmacodynamic response. Conversely, in some cases a late immune-mediated response to antibody treatment (1, 20) may be the most important factor in producing clinical benefit and thus lack of an early decrease in FDG uptake may not predict lack of benefit. Therefore, a prospective clinical trial will be required to establish the power of early FDG-PET to predict clinical benefit from anti-EGFR monoclonal antibody therapy. If early FDG-PET is proven to be predictive of clinical response, the costly practice of a protracted therapeutic trial in the majority of patients destined not to benefit can be eliminated, allowing those patients to be quickly shifted to alternative therapies, especially clinical trials of novel agents. In addition, such a trial should enhance our understanding of the mechanisms by which these biologic agents induce clinical response and provide insight as to why they are efficacious in only a minority of patients.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: G.W. Krystal, J.L. Tatum
Development of methodology: G.W. Krystal, J.L. Tatum
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): G.W. Krystal, J.L. Tatum
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): G.W. Krystal, J.L. Tatum
Writing, review, and/or revision of the manuscript: G.W. Krystal, E. Alesi, J.L. Tatum
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): G.W. Krystal, J.L. Tatum
Study supervision: J.L. Tatum

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