Original Study

Patterns of Use and Tolerance of Anti–Epidermal Growth Factor Receptor Antibodies in Older Adults With Metastatic Colorectal Cancer

Efrat Dotan,[1] Karthik Devarajan,[2] A. James D'Silva,[3] Andrew Beck,[1] Dwight D. Kloth,[4] Steven J. Cohen,[1] Crystal Denlinger[1]

Abstract

Patterns of use and tolerance of anti–epidermal growth factor receptor (EGFR) antibodies were evaluated in older patients with metastatic colorectal cancer (mCRC). Similar toxicity profiles were seen among older and younger patients. Advanced age was associated with increased use of anti-EGFR agents as monotherapy, with no association with the incidence of toxicity. These data support the use of anti-EGFR agents as clinically indicated for treatment of older patients with mCRC.

Background: Limited data are available regarding the tolerance of anti–epidermal growth factor receptor (EGFR) antibodies among elderly patients with metastatic colorectal cancer (mCRC). We retrospectively reviewed our experience of treating elderly patients with mCRC with these agents between 2004 and 2011. **Methods:** Patients with mCRC $\geq$ 65 years treated with anti-EGFR agents were included in this analysis. We recorded demographic and disease characteristics, treatment regimen and duration, *KRAS* status, and overall survival (OS). Toxicity evaluation included common hematologic and nonhematologic toxicities seen with these agents. **Results:** One hundred seventeen patients were included, with a median age at treatment initiation of 73 years (range, 65-86 years), 59% of male sex, 82% with colon primary tumors, and 51% with metastatic disease at presentation. Median time on anti-EGFR treatment was 2.4 months. Older age at treatment initiation was associated with use of anti-EGFR antibody as monotherapy versus combination therapy ($P = .0009$). Worse performance status (PS) at treatment initiation was associated with a shorter overall survival (OS) ($P = .013$) and shorter treatment duration ($P = .01$). The incidence of hematologic/nonhematologic grade ≥ 3 was 36% and 15%, respectively. No association was found between age and presence of grade ≥ 3 toxicity. Longer treatment duration and better PS at treatment initiation were the only factors associated with higher incidence of grade 3 toxicity. **Conclusion:** Our data demonstrate that anti-EGFR antibodies can be used in older patients with mCRC, with toxicity profiles similar to those reported in large phase III studies of younger patients. Advanced age was associated with receipt of anti-EGFR agents as monotherapy but did not impact treatment outcomes in this population.

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Introduction

Colorectal cancer (CRC) is generally a diagnosis of older adults, with 40% of diagnoses made in patients > 75 years and a median age of diagnosis of 71 years.[1] Twenty percent of these patients have metastatic disease at the time of diagnosis.[2] Despite the large number of older patients with metastatic CRC (mCRC) seen in clinical practice, the pivotal trials guiding clinical management include small numbers of older patients.[3] Because of the lack of

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[1]Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA
[2]Department of Biostatistics and Bioinformatics, Fox Chase Cancer Center, Philadelphia, PA
[3]Department of Internal Medicine, Temple University Hospital, Philadelphia, PA
[4]Department of Pharmacy, Fox Chase Cancer Center, Philadelphia, PA

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Address for correspondence: Efrat Dotan, MD, Department of Medical Oncology, Fox Chase Cancer Center, 333 Cottman Ave, Philadelphia, PA 19111
Fax: 215-728-3639; e-mail contact: efrat.dotan@fccc.edu

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prospective data to guide treatment decisions, the management of elderly patients with CRC is challenging.

Cetuximab and panitumumab are epidermal growth factor receptor (EGFR) inhibitors that are approved for the treatment of *KRAS* wild-type mCRC. Multiple phase III studies have demonstrated improvement in progression-free survival and overall survival (OS) with the use of anti-EGFR antibodies alone or in combination with chemotherapy in patients with wild-type *KRAS* tumors.[4-9] Only a minority of patients in these studies were > 70 years, and subgroup analyses of elderly patients demonstrated mixed efficacy results.[6,10] These drugs carry less of the typical adverse events associated with chemotherapy. However, they do carry significant toxicities, including skin rash, diarrhea, and electrolyte imbalance. Among older adults, side effects such as these can cause significant morbidity. Although skin toxicity primarily causes cosmetic discomfort, diarrhea may predispose older patients to dehydration and the risk of renal compromise.

European groups have studied the effects of these drugs on elderly patients in retrospective or small prospective studies. The largest cohort of older patients treated with anti-EGFR antibodies was reported in an observational study from Germany evaluating the efficacy and safety of these agents in 300 patients > 65 years compared with their younger counterparts. The study demonstrated similar toxicity and efficacy with the combination of cetuximab and irinotecan in older and younger patient cohorts.[11] The Spanish Group for Digestive Tumors Therapy studied cetuximab as a single agent and in combination with irinotecan or capecitabine in the older population and demonstrated a similar toxicity profile to that seen in younger patients.[12-14] We sought to evaluate the use of anti-EGFR antibodies among older patients with mCRC treated at an academic center in the United States. In this report, we outline the pattern of care for use of anti-EGFR antibodies and the toxicity profile seen among elderly patients treated with these agents.

Patients and Methods

Patient Characteristics

Patients > 65 years who had received cetuximab or panitumumab between February 2004 and March 2011 for the treatment of mCRC were identified through our pharmacy computer database. All patients had a histologically confirmed diagnosis of metastatic adenocarcinoma of the colon/rectum. We excluded patients with a histologic type other than adenocarcinoma of the colon or rectum as well as patients with incomplete medical records.

Data Collection

The following patient and disease characteristics were gathered through a retrospective review of the electronic medical record: age, sex, site of disease, stage at diagnosis, site of metastasis, number of metastatic sites, and initial PS (ECOG). We further extracted data regarding patient treatment patterns, including drugs, treatment duration, doses, line of therapy, treatment interruption, and dose reductions. We defined a line of therapy as a change in therapy secondary to disease progression. To minimize the recall bias associated with a retrospective review, we recorded objective laboratory parameters as well as subjective parameters from the patient's clinic visit provider notes. Hematologic toxicity was evaluated by review of the patient's laboratory records during the treatment period. Nonhematologic toxicity was evaluated based on medical record documentation. In addition, we reviewed parameters that can serve as surrogates for nonhematologic toxicity such as decline in PS at the end of treatment, > 10% weight loss, > 10% decrease in albumin level, use of local or systemic therapy for rash, and hospitalization. Toxicity was graded using the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The study included patients who received anti-EGFR antibodies before as well as those who received these agents after the introduction of *KRAS* testing as a predictor of response. Therefore, a significant portion of patients in this study did not have their tumors tested for this mutation. Finally, we recorded the OS of patients in our cohort from date of diagnosis to death. The study protocol was approved by the Institutional Review Board at Fox Chase Cancer Center.

Statistical Analysis

Descriptive statistics for demographic characteristics, disease presentation, and treatment-related toxicity were summarized. Continuous variables were analyzed using the Mann-Whitney test or the Kruskal-Wallis test as appropriate, and categorical variables were analyzed using the Fisher exact test. Age was analyzed as a continuous variable in our univariate analysis and as a categorical variable in the OS analysis. PS was analyzed as a categorical variable depicting 2 groups of PS 0-1 and PS 2-3. The 2-sample binomial test of proportions was used to compare proportions between different groups. All tests were 2 sided and used a 5% type I error. The R statistical language and environment (www.r-project.org) and the STATA package (StataCorp, LP, College Station, TX) were used for computations.[15] Univariate log-rank tests and Cox proportional hazards models were used to correlate treatment and demographic and clinical variables with OS. OS was calculated from date of diagnosis of CRC to date of death. Kaplan-Meier survival curves and hazard ratios (with corresponding 95% confidence intervals) were computed.

Results

Patient Characteristics and Patterns of Care

Two hundred patients > 65 years who received cetuximab or panitumumab were identified from our pharmacy database. Of these, 117 patients were eligible for the final analysis. Patients were excluded based on histologic type other than adenocarcinoma and incomplete medical records. Ninety-nine patients were treated with cetuximab and 18 were treated with panitumumab (Table 1). The median age at treatment initiation was 73 years, with a preponderance of male sex and white race. Colon cancer was the predominant primary tumor type, with metastatic disease present at diagnosis in half of the patients. At the time of treatment initiation, most patients had a PS of 0 or 1. *KRAS* testing was not available for the majority of patients, and nearly all of those patients tested were wild-type KRAS. More patients treated with cetuximab had a PS of 0 at treatment initiation compared with patients in the panitumumab arm (27.3% vs. 5.6%). Alternatively, more patients in the panitumumab arm had a PS of 1 at treatment initiation compared with patients in the cetuximab arm (77.7% vs. 47.5%). These differences did not reach statistical significance, likely because of the low number of panitumumab-treated patients.