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Original article

# Economic burden of toxicities associated with metastatic colorectal cancer treatment regimens containing monoclonal antibodies

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## Abstract

**Objectives:**
Little is known about toxicity-related costs of monoclonal antibody treatments in metastatic colorectal cancer. This study aimed to identify toxicities associated with bevacizumab, cetuximab, and panitumumab and estimate the direct costs of these toxicities.

**Methods:**
Grade 3 and 4 toxicities were identified by a comprehensive literature search. Inpatient costs were estimated using ICD-9 codes and 2007 Medicare payments from the Healthcare Cost and Utilization Project database; costs were converted to 2010 dollars. Outpatient costs were estimated by applying 2010 Medicare reimbursement rates to resource use assumptions (based on in-depth clinical interviews).

**Results:**
Toxicities associated with bevacizumab included hypertension, arterial thrombosis, hemorrhage, gastrointestinal (GI) perforation, fistula, and wound-healing complications; toxicities associated with cetuximab and panitumumab included skin rash, hypomagnesemia, and infusion reactions. The inpatient cost per event was highest for GI perforation (USD 32,443), followed by fistula (USD 29,062), arterial thrombosis (USD 20,346), and wound-healing complications (USD 13,240), while inpatient costs per event for hypomagnesemia and skin rash were among the lowest. The cost per event of toxicities treated in the outpatient setting included USD 185 for skin rash up to USD 585 for wound-healing complications.

**Limitations:**
Treatment costs of toxicities for the outpatient setting were determined using assumptions validated by clinicians, and unit costs were based on Medicare reimbursement rates, which are often lower than the reimbursement rates for commercial health insurance plans. Toxicities included were only grades 3 and 4 adverse events and might be limited by differences between clinical studies.

**Conclusions:**
Monoclonal antibodies have different toxicity profiles and the costs associated with managing these toxicities vary greatly.

## Introduction

Advances in the treatment of metastatic colorectal cancer (mCRC) have improved median survival from 6–9 months to almost 2 years, largely as a result of improvements in systemic therapy[1–3]. The introduction of monoclonal antibodies targeting the vascular endothelial growth factor (VEGF; bevacizumab) or the epidermal growth factor receptor

(EGFR; cetuximab and panitumumab) is considered a significant contributor to these improved outcomes[4–8].

The economic evaluation of monoclonal antibodies in the treatment of mCRC has been based primarily on effectiveness estimates, such as anticipated improvements in survival or tumor response rate[9,10]. While demonstrated survival benefits are key drivers for economic analysis, treatment-related toxicities are also important determinants of value. In particular, serious toxicities that lead to subsequent morbidity and mortality can place a significant burden on resources. The US and European regulatory authority-approved product information suggests that gastrointestinal (GI) perforation, surgical and wound-healing complications, hypertension, arterial and venous thromboembolism, and hemorrhage are serious events associated with bevacizumab treatment (Avastin Prescribing Information, Genentech Inc, San Francisco, CA, 2009; Avastin Summary of Product Characteristics, Roche Products Ltd, Basel, Switzerland, 2010). Inhibitors of the EGFR have been associated with skin rash, hypomagnesemia, and infusion reactions, although the rates differ between agents. Based on regulatory authority-approved product information, cetuximab (a chimeric monoclonal antibody) is associated with severe infusion reactions in ~3% of patients (Erbitux Prescribing Information, Imclone Systems Inc and Bristol Myers Squibb Company, New York and Princeton, 2009; Erbitux Summary of Product Characteristics, Merck KGaA, Darmstadt, Germany, 2010), and such reactions are observed in ~1% of patients with the fully human monoclonal antibody panitumumab (Vectibix Prescribing Information, Amgen Inc, Thousand Oaks, CA, 2008; Vectibix Summary of Product Characteristics, Amgen Ltd, Cambridge, UK, 2010).

Limited information on the cost of treatment-related toxicities associated with chemotherapies in patients with CRC is available[11,12], and, in particular, little is known about the economic burden of toxicities related specifically to monoclonal antibodies for mCRC. Knowledge of these costs are important because it can help inform evaluations of the clinical and cost-effectiveness of monoclonal antibodies for the management of patients with mCRC. The primary objective of this study was, therefore, to estimate the direct cost of toxicities associated with the use of monoclonal antibodies in the treatment of mCRC.

# Materials and methods

## Data selection

A comprehensive and systematic literature search was performed to identify clinical studies evaluating the use of bevacizumab-, cetuximab-, or panitumumab-containing treatment regimens recommended for the treatment of mCRC by the NCCN Colon Cancer and NCCN Rectal Cancer Guidelines. Studies of recommended regimens were initially identified by an ancestral search of reference lists from the 2010 NCCN Clinical Practice Guidelines in Oncology for colon cancer and for rectal cancer[13,14]. A targeted PubMed literature search, limited to phase 3 clinical trials published in the English language between 2000 and 2010, was performed. Phase 2 trials were only included when Phase 3 data were not available for that recommended regimen. PubMed search terms used included 'bevacizumab' or 'cetuximab' or 'panitumumab' combined with 'colorectal neoplasms' or 'colonic neoplasms', or 'rectal neoplasms' combined with 'neoplasm metastasis' or 'metastatic' or 'advanced'. To ensure that we included the most recent and late-breaking bevacizumab, cetuximab, and panitumumab studies, abstracts from the American Society of Clinical Oncology and European Society of Medical Oncology annual meetings (years 2008–2010) were reviewed and considered for inclusion. Studies meeting the inclusion criteria were reviewed to extract information on treatment setting, study phase, number of patients receiving monoclonal antibody treatment, treatment history, and reported grade 3–4 adverse events. Finally, regulatory-approved labels were reviewed to identify additional toxicities. Specifically, adverse events were identified from the 'Warning and Precautions' section of the Food and Drug Administration-approved prescribing information and the 'Special Warning and Precautions for Use' section of the European Medicines Agency-approved Summary of Product Characteristics for bevacizumab, cetuximab, and panitumumab (Avastin PI 2009; Erbitux PI 2009; Vectibix PI 2008; Avastin SPC 2010; Erbitux SPC 2010; Vectibix SPC 2010).

## Determination of the costs of treating toxicities

Since the same or similar toxicities can be reported using different terminology in different clinical trials or product labels, the adverse events identified were placed into representative groupings based on similarities in the event type and, hence, anticipated similarities in the treatment approach, as determined by clinical expert opinion from a panel of two oncologists and one cardiologist. Within each group, the most clinically significant toxicity (as identified by clinical experts) was selected as the 'representative' adverse event, and this was then used to estimate the direct cost of treatment. Inpatient and outpatient costs were estimated for each representative adverse event. The exception to this was for those events which, according to clinician opinion, would always be treated on an inpatient basis when presenting acutely, and for which only inpatient costs were calculated. The costs were based on a US payer perspective and were estimated

 

from reimbursed amounts for services delivered, reported in 2010 dollars.

### Inpatient costs

The costs of toxicities if they were treated in the inpatient setting were estimated using inpatient costs from the 2007 Healthcare Cost and Utilization Project (HCUP) nationwide inpatient sample (NIS) database, the largest US all-payer inpatient care database[15]. The NIS contains discharge-level records of the total cost of each hospital stay, including drugs and devices. The primary International Classification of Diseases, 9th Revision (ICD-9)[16] codes were identified for the 'representative' toxicities using Flash Code™, a medical billing/coding database, and all codes were checked and validated by a clinician. The mean 2007 unit cost of each inpatient event, based on ICD-9 codes, was then identified from the HCUP NIS database. Costs were converted to 2010 dollars using the Consumer Price Index for medical care services (Bureau of Labor Statistics website).

### Outpatient costs

The outpatient cost of each representative toxicity was based on the total cost of healthcare resources used for treating that event if the toxicity were to be treated in the outpatient setting. Use of resources was determined by in-depth clinical interviews with a panel of two oncologists and one cardiologist. Resources included office visits, laboratory tests, and procedures. However, costs of drugs that were used in the outpatient setting to treat toxicities were not included. Current Procedural Terminology (CPT) codes were determined for each resource and were used to identify the corresponding unit costs of those resources, based on the Medicare physician fee schedule, identified from the 2010 national average payment amount[17]. Outpatient treatment costs were calculated as the sum of the unit costs of all resource assumptions for treating that toxicity. For example, when an anemia event was assumed to be treated in the outpatient setting, an initial physician visit, two complete blood counts, and a follow-up physician visit would be required to treat this event. The outpatient cost for an anemia event would therefore be calculated as (2× unit cost for a physician visit) + (2 ×unit cost for a complete blood count laboratory test).

## Results

### Data sources and severe toxicities identified

Twenty publications of clinical trials met the inclusion criteria, of which 16 were phase 3 clinical trials, one reported a combined analysis of phase 2 and 3 studies, and three were phase 2 (Table 1). The way in which grade 3–4 adverse events were reported varied between clinical trials and publications: some reported 'adverse events of interest', while others reported 'selected adverse events', 'most frequently observed adverse events', adverse events reported in a specified period of time, and adverse events reported in ≥3% of patients. Among all studies, 16 reported grade 3 and 4 adverse events together and four reported grade 3 and 4 adverse events separately.

A total of 60 grade 3–4 adverse events were identified from clinical studies and product labels (Table 2). A number of these (including thrombocytopenia, diarrhoea, vomiting, abdominal pain, and hand–foot syndrome) were reported in association with regimens containing each of the monoclonal antibodies. Severe toxicities associated with bevacizumab included GI perforation, fistula, hemorrhage, wound-healing complications, hypertension, reversible posterior leukoencephalopathy syndrome (RPLS), arterial and venous thromboembolic events, congestive heart failure, proteinuria, neutropenia and infections, and hypersensitivity reactions/infusion reactions (Avastin PI 2009; Avastin SPC 2010)[2,28,29,31]. Severe toxicities associated with the use of the EGFR inhibitors, cetuximab and panitumumab, included infusion reactions, interstitial lung disease/pulmonary fibrosis, dermatologic toxicity (skin rash), and hypomagnesemia, although rates of these toxicities differed between the two drugs (Erbitux PI 2009; Vectibix PI 2008; Erbitux SPC 2010; Vectibix SPC, 2010)[6,20,21,24,26].

### Costs of treating severe toxicities

The severe toxicities identified were categorized into 23 groups for the determination of treatment costs based on clinical expert opinion from a panel of two oncologists and one cardiologist, as illustrated in Table 2. Some events were grouped together (for example, cardiac and cerebrovascular ischemia, left ventricular dysfunction, thromboembolism, and arterial thromboembolic event), while others (such as wound-healing complication and hypomagnesemia) were considered individually.

#### Inpatient costs

The estimated inpatient costs of treating each toxicity are shown in Table 3. The highest inpatient cost per event was for GI perforation (USD 32,443), followed by fistula (USD 29,062), arterial thromboembolic event (USD 20,346), wound-healing complication (USD 13,240), hemorrhage (USD 12,956), and infusion reaction (USD 10,877). The inpatient cost per event for hypomagnesemia and skin rash were among the lowest (USD 6174 and 4424, respectively).

Table 1. Summary of clinical studies of bevacizumab, cetuximab, or panitumumab for the treatment of mCRC in which associated grade 3–4 toxicities were reported.

| Regimen | Reference | Study setting | Phase | Sample size | Treatment history |
|---|---|---|---|---|---|
| Cetuximab | Pessino *et al.*[18] | 1st line | 2 | 39 | NA |
| | Cunningham *et al.*[19] | 2nd line/3rd line | 3 | 111 | Irinotecan-based regimen |
| | Jonker *et al.*[20] | 2nd line/3rd line | 3 | 288 | Fluoropyrimidine, irinotecan and oxaliplatin |
| Panitumumab | Van Cutsem *et al.*[21] | 3rd line | 3 | 231 | Fluoropyrimidine, irinotecan and oxaliplatin |
| 5-FU/LV + bevacizumab | Hurwitz *et al.*[22] | 1st line | 3 | 110 | NA |
| | Kabbinavar *et al.*[5] | 1st line | 2/3 | 249 | NA |
| IFL + bevacizumab | Hurwitz *et al.*[2] | 1st line | 3 | 402 | NA |
| Irinotecan-based chemotherapy + bevacizumab | Hecht *et al.*[23] | 1st line | 3 | 113 | NA |
| Irinotecan + cetuximab | Sobrero *et al.*[24] | 2nd line | 3 | 648 | Fluoropyrimidine and oxaliplatin |
| | Cunningham *et al.*[19] | 2nd line/3rd line | 3 | 218 | Oxaliplatin and irinotecan |
| FOLFIRI + cetuximab | Van Cutsem *et al.*[6] | 1st line | 3 | 599 | NA |
| | Koo *et al.*[25] | 3rd line | 2 | 31 | Fluoropyrimidine, irinotecan and oxaliplatin |
| FOLFIRI + panitumumab | Karthaus M *et al.* (Presented at Gastrointestinal Cancers Symposium 2009. Abstract 388) | 1st line | 2 | 154 | NA |
| | Peeters M *et al.*[26] | 2nd line | 3 | 541 | Oxaliplatin and bevacizumab |
| Oxaliplatin-based chemotherapy + bevacizumab | Hecht *et al.*[23] | 1st line | 3 | 397 | NA |
| CapeOx + bevacizumab | Hochster *et al.*[27] | 1st line | 3 | 72 | NA |
| | Saltz *et al.*[28] | 1st line | 3 | 349 | NA |
| | Tol *et al.*[29] | 1st line | 3 | 368 | NA |
| CapeOx + cetuximab | Adams *et al.*[30] | 1st line | 3 | 166 | NA |
| FOLFOX4 + bevacizumab | Saltz *et al.*[28] | 1st line | 3 | 349 | NA |
| | Giantonio *et al.*[31] | 2nd line | 3 | 287 | Fluoropyrimidine and irinotecan |
| FOLFOX4 + cetuximab | Bokemeyer *et al.*[4] | 1st line | 3 | 170 | NA |
| FOLFOX4 + panitumumab | Douillard *et al.*[8] | 1st line | 3 | 593 | NA |
| mFOLFOX6 + bevacizumab | Hochster *et al.*[27] | 1st line | 3 | 71 | NA |

NA, not available.

### Outpatient costs

Unit costs for the individual resources used for the treatment of toxicities in the outpatient setting are provided in Table 4. These varied from laboratory fees of USD 4.54 for a urinalysis test to USD 370.59 for professional fees associated with computed tomography scanning.

The resources used for determining the costs of treating each toxicity in the outpatient setting (based on in-depth clinical interviews) and the corresponding total costs are shown in Table 5. Outpatient costs of toxicities depended on the nature and extent of the resources used; for example, skin toxicity and hypertension (each requiring two physician visits) were estimated to cost USD 185, whereas a wound-healing complication requiring more substantial resources, including imaging equipment and devices, was estimated to cost USD 585. It was worth noting that costs of drugs that were used in the outpatient setting to treat toxicities were not included in the outpatient treatment costs.

## Discussion

The monoclonal antibodies bevacizumab, cetuximab, and panitumumab have distinct and well-defined tolerability profiles in the treatment of mCRC. Most notably, bevacizumab is associated with GI perforation, non-GI fistula formation, hemorrhage, wound-healing complications, hypertension, arterial and venous thromboembolic events, and RPLS (Avastin PI 2009; Avastin SPC 2010)[2,28,29,31], while cetuximab and panitumumab are associated with infusion reactions, dermatologic toxicity, and hypomagnesemia (although with different incidence rates) (Erbitux PI 2009; Vectibix PI 2008; Erbitux SPC 2010; Vectibix SPC 2010)[6,19,21,26]. Our analysis illustrates that the cost of treating these toxicities varied substantially depending on the event itself, and whether it would be severe enough to warrant inpatient care. Understandably, the most costly events were those that required the most significant inpatient resources: this included GI perforation, fistula, arterial thromboembolic

 

Table 2. Grouping of severe toxicities identified in association with bevacizumab, cetuximab, and panitumumab.

| Representative event[a] | Other adverse events within the group[b] |
|---|---|
| Anemia | Thrombocytopenia |
| Arterial thromboembolic event | Cardiac ischemia, cerebrovascular ischemia, left ventricular dysfunction, thromboembolism |
| Hemorrhage | |
| Deep vein thrombosis | Deep vein thrombophlebitis, venous thrombotic event, thrombotic event |
| Dyspnea | |
| Failure to thrive | Anorexia, fatigue, weight loss |
| Febrile neutropenia | Infection (NOS), leukopenia, neutropenia |
| Fistula | Intestinal obstruction, fistula/intra-abdominal abscess, intra-abdominal thrombosis |
| Gastrointestinal perforation | |
| Hypertension | |
| Hypomagnesemia | |
| Infusion reaction | Hypersensitivity reaction |
| Interstitial lung disease | |
| Peripheral edema | Edema, hypocalcaemia, hypokalemia |
| Peripheral neuropathy | Asthenia, neuropathy, neurologic toxicity paresthesia, sensory neuropathy |
| Proteinuria | |
| Pulmonary embolism | |
| Renal failure | |
| Reversible posterior leukoencephalopathy syndrome | |
| Skin rash | Mucositis, stomatitis, skin toxicity, skin exfoliation, hand–foot syndrome, paronychia, skin and subcutaneous (all) |
| Urinary tract infection | |
| Vomiting | Abdominal pain, constipation, diarrhea, dehydration |
| Wound-healing complication | |

[a]The representative toxicity was the most clinically significant event within that grouping (as determined by clinical opinion) on which the costs of the toxicities in the group were based.
[b]Toxicities were grouped based on anticipated similarities in treatment approach, as determined by clinical opinion.
NOS, not otherwise specified.

events, and hemorrhage, events that were considered by clinicians to always require inpatient care. Severe infusion reactions and wound-healing complications would also be relatively costly to treat on an inpatient basis. Skin toxicity, hypomagnesemia and hypertension were relatively less costly events to treat, particularly when they could be managed in an outpatient setting. It was worth noting that some events, such as GI perforation, have a much lower rate compared to the less costly events, such as dermatologic toxicities.

There are a number of limitations to our analysis. The treatment costs of toxicities for the outpatient setting were determined by resources used, which were based on

Table 3. Inpatient costs of treating severe toxicities associated with the use of the monoclonal antibodies bevacizumab, cetuximab, and panitumumab in metastatic colorectal cancer.

| Toxicity | ICD-9 code | Inpatient costs (2010 USD) |
|---|---|---|
| Anemia | 285.22 | 6219 |
| Arterial thromboembolic event | 444.22 | 20,346 |
| Deep vein thrombosis | 451.41 | 8748 |
| Dyspnea | 786.05 | 5582 |
| Failure to thrive | 783.7 | 8104 |
| Febrile neutropenia | 288.03 | 12,606 |
| Fistula | 537.4 | 29,062 |
| Gastrointestinal perforation | 569.83 | 32,443 |
| Hemorrhage | 459 | 12,956 |
| Hypertension | 405.99 | 8453 |
| Hypomagnesemia | 275.2 | 6174 |
| Infusion reaction | N/A | 10,877* |
| Interstitial lung disease | 515 | 13,001 |
| Peripheral edema | 782.3 | 5695 |
| Peripheral neuropathy | 357.6 | 13,113 |
| Proteinuria | 791.0 | 4618 |
| Pulmonary embolism | 415.19 | 11,411 |
| Renal failure | 584.9 | 10,688 |
| Reversible posterior leukoencephalopathy syndrome | 348.5 | 10,116 |
| Skin rash | 782.1 | 4424 |
| Urinary tract infection | 599.0 | 6890 |
| Vomiting | 787.01 | 5559 |
| Wound-healing complication | 998.32 | 13,240 |

*Costs based on Foley *et al.*[32] as no ICD-9 code was available for this event.

Table 4. Unit costs for resources used to determine the costs of toxicities in the outpatient setting.

| Resource | CPT code | Unit cost (2010 USD) | Fee type |
|---|---|---|---|
| Basic metabolic panel | 80047 | 12.12 | Lab fee |
| Complete blood count | 85025 | 11.14 | Lab fee |
| Chest X-ray | 71030 | 46.17 | Professional fee |
| Computed tomography scan | 70450 | 193.05 | Professional fee |
| | 72125 | 253.31 | Professional fee |
| | 70488 | 370.59 | Professional fee |
| Electrocardiogram | 93000 | 30.92 | Professional fee |
| | 93010 | 9.02 | Professional fee |
| Electrolytes | 80051 | 10.05 | Lab fee |
| Medical stocking | A6531 | 45.43 | Durable medical equipment fee |
| Physician visit, moderate complexity | 99212 | 38.97 | Professional fee |
| | 99214 | 92.33 | Professional fee |
| | 99215 | 132.79 | Professional fee |
| Platelets | 85025 | 11.14 | Lab fee |
| Protime | 85610 | 5.62 | Lab fee |
| Renal function test | 78596 | 342.63 | Professional fee |
| Spirometry | 94010 | 32.84 | Professional fee |
| Thyroid function test | 78006 | 240.78 | Professional fee |
| | 78007 | 124.49 | Professional fee |
| | 84479 | 9.27 | Lab fee |
| Tissue culture | 88233 | 201.57 | Lab fee |
| Ultrasound | 37250 | 111.45 | Professional fee |
| | 37251 | 85.52 | Professional fee |
| Urinalysis | 81001 | 4.54 | Lab fee |
| Vacuum closure system | 97606 | 40.05 | Professional fee |
| | A7043 | 36.02 | Durable medical equipment fee |

Table 5. Outpatient costs of treating severe toxicities associated with the use of the monoclonal antibodies bevacizumab, cetuximab, and panitumumab in metastatic colorectal cancer.

| Toxicity | Resource use assumptions* | Outpatient cost (2010 USD) |
|---|---|---|
| Anemia | 2× physician visit; 2× complete blood count | 207 |
| Dyspnea | 3× physician visit; 2× spirometry | 343 |
| Failure to thrive | 2× physician visit; 1× complete blood count; 1× electrolytes; 1× thyroid function test | 447 |
| Febrile neutropenia | 2× physician visit; 2× complete blood count; 1× electrolytes | 217 |
| Hypertension | 2× physician visit | 185 |
| Hypomagnesemia | 2× physician visit; 2× electrolytes | 205 |
| Infusion reaction | 2× physician visit; 1× complete blood count; 1× electrocardiogram; 1× urinalysis; 1× renal function test | 327 |
| Peripheral edema | 2× physician visit; 1× electrolytes; 1× medical stocking; 1× thyroid function test | 481 |
| Peripheral neuropathy | 2× physician visit | 185 |
| Proteinuria | 2× physician visit; 1× urinalysis; 1× basic metabolic panel | 201 |
| Skin rash | 2× physician visit | 185 |
| Urinary tract infection | 1× physician visit; 1× complete blood count | 103 |
| Vomiting | 2× physician visit; 1× electrolytes | 195 |
| Wound-healing complication | 2× physician visits; 1× tissue culture; 1× complete blood count; 1× ultrasound; 1× vacuum closure system | 585 |

Based on clinical expert opinion, arterial thromboembolic event, hemorrhage, deep vein thrombosis, fistula, gastrointestinal perforation, interstitial lung disease, pulmonary embolism, renal failure, and reversible posterior leukoencephalopathy syndrome were all assumed to be treated on an inpatient basis only.
*Based on in-depth clinical interview.

assumptions validated by clinicians. Although these may not always reflect clinical practice at an event level they will be representative at a population level. However, only office visits, laboratory tests, and procedures were considered for outpatient resources, and thus the outpatient costs of some toxicities frequently treated with drugs may have been underestimated. Additionally, unit costs for outpatient services were based on Medicare reimbursement rates, which are often lower than the reimbursement rates for commercial health insurance plans. This may have also led us to underestimate the outpatient costs for toxicities. For inpatient costs, however, use of the NIS database meant that our analysis captured the total costs of the hospital stay, including drugs and devices; although these costs were estimated based on the general population, not based on mCRC patients specifically. Furthermore, the most clinically significant toxicity (as identified by clinical experts) was selected as the 'representative' adverse event, and this was then used to estimate the direct cost of treatment; however, the costs for treating these events in the same group might differ.

In terms of the toxicities identified by our search, ensuring a comprehensive and standardized list of severe toxicities was limited by differences between studies in the approach used to define and report grade 3–4 adverse events, the varied sample sizes among studies, variation in patient characteristics, and especially uncertainty regarding the consistency of the naming of adverse events. In addition, our focus was only on identifying the more severe toxicities (grades 3 and 4). We did not capture information on grade 1–2 adverse events reported in clinical trials, although these, by definition, do not require intensive medical intervention. Finally, the evaluated treatment regimens were used in different lines (from 1st line to 3rd line) of therapy, and the treatment populations were not the same for the three targeted agents, such as cetuximab and panitumumab, are restricted to EGFR-expressing and wild-type *KRAS* mCRC patients.

To our knowledge, this is the first study to evaluate the costs of treating severe toxicities associated with monoclonal antibodies for mCRC. Monoclonal antibodies have different toxicity profiles and the estimated costs associated with managing these toxicities vary greatly. Knowledge of these costs can help inform evaluations of the clinical and cost-effectiveness of monoclonal antibodies for the management of patients with mCRC.

## Transparency

**Declaration of funding**
This study was funded by Amgen Inc. All authors had full access to the data and had final responsibility for the decision to submit the manuscript.

**Declaration of financial/other relationships**
ZZ, SG, and BB have disclosed that they are employees of Amgen Inc. CB, JM, and KT have disclosed that they are employees of IMS Consulting Group, a company that received funding from Amgen Inc to perform the analyses reported in this manuscript.

 

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## References

1. Goldberg RM, Sargent DJ, Morton RF, et al. A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J Clin Oncol 2004;22:23-30
2. Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335-42
3. Kelly H, Goldberg RM. Systemic therapy for metastatic colorectal cancer: current options, current evidence. J Clin Oncol 2005;23:4553-60
4. Bokemeyer C, Bondarenko I, Makhson A, et al. Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 2009;27:663-71
5. Kabbinavar FF, Hambleton J, Mass RD, et al. Combined analysis of efficacy: the addition of bevacizumab to fluorouracil/leucovorin improves survival for patients with metastatic colorectal cancer. J Clin Oncol 2005;23:3706-12
6. Van Cutsem E, Köhne CH, Hitre E, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 2009; 360:1408-17
7. Van Cutsem E, Nordlinger B, Cervantes A. ESMO Guidelines Working Group. Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. Ann Oncol 2010;21(5 Suppl):v93-7
8. Douillard JY, Siena S, Caissdy J, et al. Randomised, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as a first-line treatment in patients with previously untreated metastatic colorectal cancer: the prime study. J Clin Oncol 2010;28:4697-705
9. Starling N, Tilden D, White J, et al. Cost-effectiveness analysis of cetuximab/irinotecan vs active/best supportive care for the treatment of metastatic colorectal cancer patients who have failed previous chemotherapy treatment. Br J Cancer 2007;96:206-12
10. Tappenden P, Jones R, Paisley S, et al. The cost-effectiveness of bevacizumab in the first-line treatment of metastatic colorectal cancer in England and Wales. Eur J Cancer 2007;43:2487-94
11. Chu E, Schulman KL, Zelt S, et al. Costs associated with complications are lower with capecitabine than with 5-fluorouracil in patients with colorectal cancer. Cancer 2009;115:1412-23
12. Dranitsaris G, Maroun J, Shah A. Estimating the cost of illness in colorectal cancer patients who were hospitalized for severe chemotherapy-induced diarrhea. Can J Gastroenterol 2005;19:83-7
13. NCCN clinical practice guidelines in oncology: colon cancer, 2010 (V.3.2010). http://www.nccn.org/professionals/physician_gls/PDF/colon.pdf. Accessed August 2010
14. NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer, 2010 (V.3.2010). http://www.nccn.org/professionals/physician_gls/PDF/rectal.pdf. Accessed August 2010
15. HCUP Fee Schedule 2007. http://hcupnet.ahrq.gov/. Accessed August 2010
16. The International Classification of Diseases, 9th Revision (ICD-9) 2010. www.flashcode.com. Accessed August 2010
17. US DHHS, Centers for Medicare and Medicaid services. CMS Fee Schedule 2010. http://www3.cms.gov/PhysicianFeeSched/. Accessed July 2010
18. Pessino A, Artale S, Sciallero S, et al. First-line single-agent cetuximab in patients with advanced colorectal cancer. Ann Oncol 2008;19:711-6
19. Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337-45
20. Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med 2007;357:2040-8
21. Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25:1658-64
22. Hurwitz HI, Fehrenbacher L, Hainsworth JD, et al. Bevacizumab in combination with fluorouracil and leucovorin: an active regimen for first-line metastatic colorectal cancer. J Clin Oncol 2005;23:3502-8
23. Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol 2009;27:672-80
24. Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:2311-9
25. Koo DH, Lee JL, Kim TW, et al. A Phase II study of cetuximab (Erbitux) plus FOLFIRI for irinotecan and oxaliplatin-refractory metastatic colorectal cancer. J Korean Med Sci 2007;22(Suppl):S98-S103
26. Peeters M, Price T, Cervantes A, et al. Randomised phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol 2010;28:4706-13
27. Hochster HS, Hart LL, Ramanathan RK, et al. Safety and efficacy of oxaliplatin and fluoropyrimidine regimens with or without bevacizumab as first-line treatment of metastatic colorectal cancer: results of the TREE Study. J Clin Oncol 2008;26:3523-9
28. Saltz LB, Clarke S, Díaz-Rubio E, et al. Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. J Clin Oncol 2008;26:2013-9
29. Tol J, Koopman M, Cats A, et al. Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. N Engl J Med 2009;360:563-72
30. Adams RA, Meade AM, Madi A, et al. Toxicity associated with combination oxaliplatin plus fluoropyrimidine with or without cetuximab in the MRC COIN trial experience. Br J Cancer 2009;100:251-8
31. Giantonio BJ, Catalano PJ, Meropol NJ, et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. J Clin Oncol 2007;25:1539-44
32. Foley KA, Wang PF, Barber BL, et al. Clinical and economic impact of infusion reactions in patients with colorectal cancer treated with cetuximab. Ann Oncol 2010;21:1455-6