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ORIGINAL ARTICLE

Risk of oral and gastrointestinal mucosal injury among patients receiving selected targeted agents: a meta-analysis

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Abstract
Purpose The purpose of this study was to estimate the risk and severity of oral and gastrointestinal mucosal toxicities associated with selected targeted agents.
Methods We searched the English-language literature in February 2011 for reports of randomized clinical trials comparing a FDA-approved targeted agent to a standard of care regimens. Long-term follow-up and secondary reports of trials were excluded, leaving 85 studies for analysis. Using meta-analytic methods, we calculated the relative risks of oral and gastrointestinal toxicities, adjusting for sample size using the inverse variance technique. For each targeted agent and each side effect, we calculated the number needed to harm, the number of patients that, if treated with the more toxic regimen, would produce one additional episode of the toxicity.
Results Oral mucositis was significantly more frequent among patients treated with bevacizumab, erlotinib, sorafenib, or sunitinib, although this difference was confined to low-grade mucositis. The clinical significance of these findings is unclear given its low incidence and mild severity. In contrast, diarrhea was significantly more frequent with most of the targeted agents studied, with adjusted relative risks between 1.5 and 4.5. An additional patient with diarrhea will be observed for every three to five patients treated with these targeted agents, compared with conventional regimens.

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Conclusions Oral mucosal toxicities occasionally complicate treatment with these targeted agents, but the clinical significance of this finding is not clear. Diarrhea is a hallmark of treatment with these targeted agents; this side effect should be carefully ascertained to permit early intervention and control.

Keywords Mucositis · Stomatitis · Diarrhea · Targeted therapy · Toxicity · Meta-analysis · Systematic review

Introduction

Oral and gastrointestinal mucosal injuries commonly complicate antineoplastic chemo- and radiation therapy. These complications disrupt delivery of planned therapy and adversely affect quality of life, utilization of healthcare resources, and the cost of care [1–5]. The MASCC/ISOO Clinical Practice Guideline for the Prevention and Treatment of Mucositis was developed to provide recommendations for the prevention and management of these significant complications [6, 7]. In concert with the current update of those guidelines, we reviewed the risks of these complications associated with selected targeted agents.

Over the past 15 years, targeted therapies, which include monoclonal antibodies and small molecule inhibitors, have significantly changed the treatment of cancer [4, 8]. Many are routinely used to treat common malignancies, including breast, colorectal, gastric, lung, head and neck, lymphoma, leukemia, pancreatic, and multiple myeloma. Targeted therapy improves survival but toxicities remain [9, 10].

The adverse effects caused by targeted agents include fatigue, diarrhea, rash, nausea, cardiovascular toxicity, neutropenia, and mucositis [4]. Clinical trials of targeted agents have reported these toxicities, but with the exception of cutaneous toxicities [11], systematic examinations of their risks and severity are lacking. Furthermore, the sample sizes achieved in individual trials rarely support the examination of the risk of rarely occurring adverse events. As utilization of targeted agents continues to expand, such a systematic evaluation is critical to understanding the effectiveness and harms associated with these agents. To fulfill this need, we conducted a meta-analysis of clinical trials of Food and Drug Administration (FDA)-approved targeted agents to estimate their incremental risks and severity of oral and gastrointestinal mucosal toxicities.

Methods

Search strategy

We identified studies of 26 targeted cancer therapy drugs approved by FDA as of November 2010 (Table 1) that had been published in English between January 1, 2000 and February 28, 2011 in MEDLINE [12]. Keywords used were phase II or III randomized control trials, drug names (brand or generic), and their FDA-approved indications (Table 1). Gefitinib was withdrawn from the market in the USA on April 25, 2012 [13], midway through our analysis. However, since it continues to be used in the European Union, we have included it in this report [14]. We only included studies reporting the results of trials that compared targeted and standard of care regimens. In some cases, the standard of care was no therapy (post-adjuvant therapy of breast cancer or

Table 1 FDA-approved targeted therapies for cancer

Drug name	Approved indication
Alemtuzumab	B-cell CLL
Bevacizumab	Glioblastoma, NSCLC, met CRC, breast cancer
Bexarotene	CTCL
Bortezomib	Multiple myeloma, mantle cell lymphoma
Cetuximab	CRC, SCCHN
Dasatinib	CML, ALL
Denileukin difitox	CTCL
Erlotinib	NSCLC, pancreatic cancer
Everolimus	Advanced RCC, subependymal giant cell astrocytoma, pancreatic neuroendocrine tumors
Gefitinib	NSCLC
Ibritumomab	NHL
Imatinib	GIST, leukemia
Lapatinib	Advanced or metastatic breast cancer
Nilotinib	CML
Ofatumumab	CLL
Panitumumab	Met CRC
Pazopanib	Advanced RCC
Pralatrexate	Peripheral T-cell lymphoma
Rituximab	NHL
Romidepsin	CTCL
Sorafenib	Advanced RCC, hepatocellular carcinoma
Sunitinib	Met RCC, GIST
Temsirolimus	Advanced RCC
Tositumomab	NHL
Trastuzumab	Breast
Vorinostat	CTCL

Source: Targeted Cancer Therapies—Fact Sheet. http://www.cancer.gov/cancertopics/factsheet/Therapy/targeted. Accessed November 2010. This is a list of targeted therapies that were approved by FDA in 2010. However, there are other agents and indications being added to or removed from the list since then

ALL acute lymphoblastic leukemia, *AML* acute myeloid leukemia, *CML* chronic myelogenous leukemia, *CRC* colorectal cancer, *CTCL* cutaneous T-cell lymphoma, *GIST* gastrointestinal stromal tumors, *NHL* non-Hodgkin's lymphoma, *HN* head and neck cancer, *NSCLC* non-small cell lung cancer, *RCC* renal cell carcinoma, *SCCHN* squamous cell carcinoma of the head and neck

renal cell carcinoma). In those cases, the comparison is to placebo or no therapy. In most cases, the targeted regimen included conventional chemotherapy, reflecting common practice. In a few cases, most notably with the agent gefitinib, the targeted agent alone was compared with chemotherapy. Studies reporting results from interim or subset analysis, phase I and early phase II dose-findings studies, those without a control group receiving standard of care regimens, and those without toxicity data were excluded.

Data extraction

We recorded information about trial design, regimen, and oral and/or gastrointestinal mucosal toxicity for each study. Trial design included trial phase (II, III, and II–III). Treatment regimen information contained regimen (targeted therapy, chemotherapy, and/or radiotherapy) and total number of patients in each arm. Mucosal side effects included oral mucositis (OM) or stomatitis, oral and aphthous ulcers, esophagitis, diarrhea, gastritis, GI perforation/hemorrhage, and xerostomia. The toxicity assessment method, assessment frequency, total number of all-grade side effects, number of high-grade (grade 3/4/5) side effects, number of hospitalizations, and number of deaths were recorded.

Statistical analysis

Meta-analysis was performed using Comprehensive Meta-Analysis version 2 (CMA). Our analytical goal was to estimate the unique contribution of the targeted agent to the risk of mucosal complications. To achieve this, we first calculated the risk of each side effect for each trial as well as the overall adjusted risk for each drug as a weighted average of risk from different studies, where the weights were estimated using the inverse-variance method. We then calculated the risk difference between the targeted regimen and the standard of care regimen. Finally, we computed the relative risk of mucosal complications for each agent. We utilized a classic half-integer continuity correction to calculate relative risk and variance for studies reporting no events in the treatment or control group. The relative risks and their corresponding 95 % confidence intervals were derived from CMA. Number needed to harm (NNH), the reciprocal of the adjusted risk increase, was calculated to examine adverse events of targeted drugs [15].

For meta-analysis of each drug, Cochran's Q statistic was calculated for assessing the heterogeneity of the trials included. The assumption of homogeneity was considered invalid when the p value is less than 0.1, and the pooled estimate calculated based on random-effects model was used. Otherwise, results from both fixed-effects and random-effects models were considered. A two-tailed p value of less than 0.05 was considered to be statistically significant.

As previously mentioned, some control regimens involved no therapy, reflecting the standard of care. These studies were combined with others for analysis, but to account for the impact of this difference on the estimates of risk, we computed risk differences and relative risks rather than absolute risk. Relative risk and risk differences should provide accurate measures of the unique contribution of the targeted agent to any regimen (no therapy or chemotherapy) except in the case where the risk of mucosal complications with targeted plus conventional chemotherapy is multiplicative (rather than additive). We are not aware of any research suggesting such a relationship. In a few studies, particularly those involving gefitinib, single-agent targeted therapy was compared with conventional chemotherapy. The inaccuracy introduced by those studies is not controlled by the use of relative risk and risk differences. In that situation, we have provided two estimates, one for all studies combined and one from a parallel analysis that excluded single agent targeted therapy versus chemotherapy.

Results

Our planned search yielded 2,179 potentially relevant articles. After excluding review articles, economic evaluation articles, case reports, commentaries, single-arm trials, and phase I trials, as planned, 101 articles were identified for review [16–116]. Of these 101 articles, 20 were excluded for being follow-up or maintenance studies, or having no more than two studies associated with the targeted drug [40, 52, 70, 73–75, 77, 89, 96, 100, 104, 106, 109–116]. At the conclusion of the planned search strategy, a total of 81 articles describing trials of eight targeted drugs remained (Fig. 1). The targeted agents included bevacizumab, cetuximab, erlotinib, gefitinib, lapatinib, rituximab, sorafenib, and trastuzumab. However, review of the excluded articles revealed the elimination of two agents considered of such clinical importance that their exclusion would be inappropriate. Consequently, we included two additional targeted agents, imatinib and sunitinib, each of which had only two qualified studies [109, 113–115]. With these additions, a total of 85 articles were included. The majority of the trials used either National Cancer Institute Common Toxicity Criteria versions 1, 2, or 3 to assess the severity of side effects, while a few trials used WHO Toxicity Criteria or National Cancer Institute of Canada Common Toxicity Criteria.

Oral mucositis or stomatitis

Based on analysis of 35 and 38 trials reporting all-grade and high-grade OM, respectively, we conclude that OM is not a clinically important feature of treatment with the targeted agents studied (Table 2). A higher risk of all-grade OM was

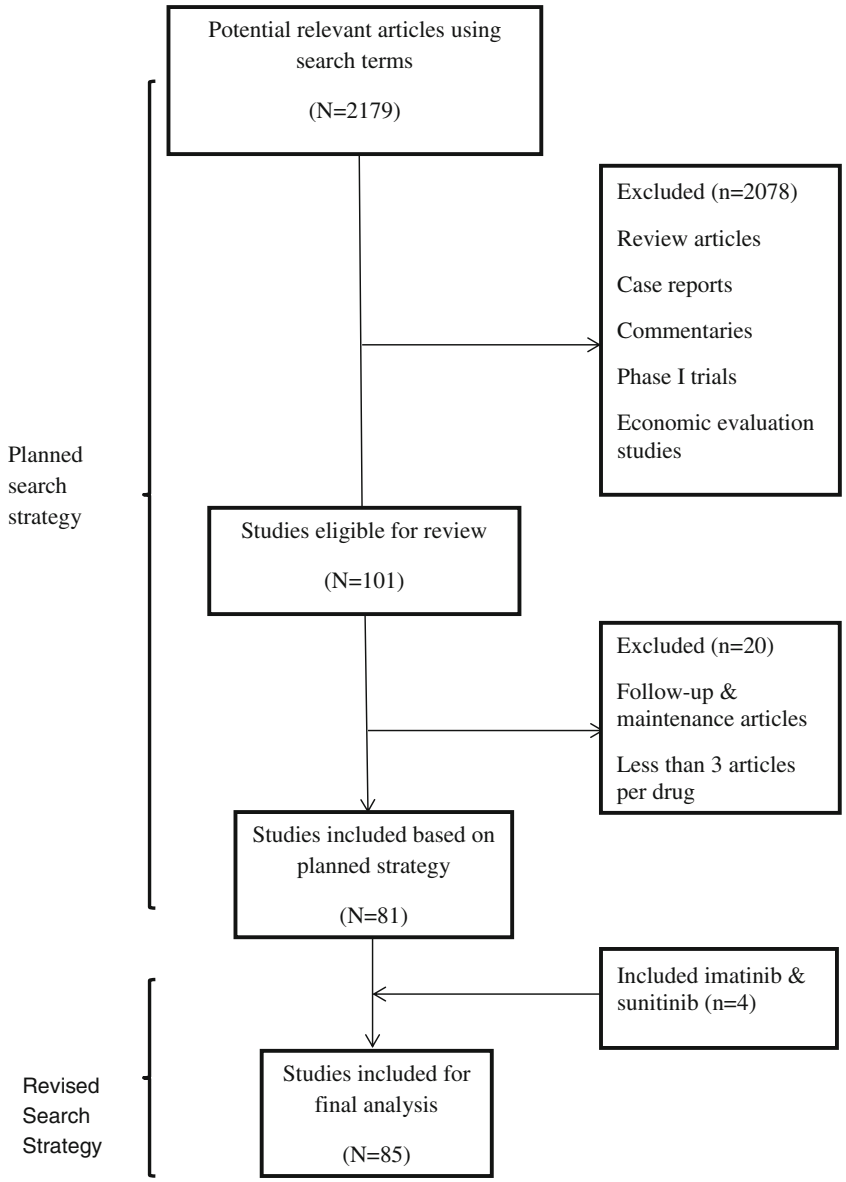

Fig. 1 Flow chart of literature search and trial selection process

observed for four of the agents. However, as described below, the increased rate was confined to low-grade OM while the rates of high-grade OM were not significantly different. In fact, for several of the targeted agents, the rates were lower than those observed for standard regimens. Thus, despite the higher frequency of low-grade OM, the clinical significance of this observation is not clear. Parallel analyses of subsets of studies excluding those examining single-agent targeted therapy versus chemotherapy showed very consistent results when compared with analyses including all studies.

Specifically, four agents showed statistically significantly greater risks of having all-grade OM, namely bevacizumab (adjusted RR=1.8, $p<0.0001$), erlotinib (adjusted RR=3.2, $p<0.01$), sorafenib (adjusted RR=3.3, $p=0.001$), and sunitinib (RR=7.7, $p<0.0001$) [23, 24, 29, 30, 35, 43–46, 92, 93, 114, 115]. For every five patients treated with bevacizumab, there was one additional all-grade OM compared to those patients in the control regimens. There was one additional all-grade OM for every nine patients treated with erlotinib compared to those in the control regimens. There was one additional all-grade OM for every four patients treated with sunitinib compared to those in the control regimens. In contrast, the adjusted risk of all-grade OM was significantly lower in the imatinib regimen compared to control regimen (RR=0.2, $p<0.0001$) [113]. As previously mentioned, the clinical significance of these differences is unclear as they are limited to relatively few cases of mild OM. With respect to other targeted drugs, there was no significant difference between targeted and control regimens for all-grade OM.

Table 2 Relative risk of all-grade and high-grade oral mucositis among patients receiving targeted therapy drugs

Drug	All-grade oral mucositis					High-grade oral mucositis				
	No. of Studies	No. of patients	Adjusted risk difference estimates (%)	Relative risk (95 % CI)[b]	No. needed to harm (NNH)[c]	No. of studies	No. of patients	Adjusted risk difference estimate (%)	Relative risk (95 % CI)	No. needed to harm (NNH)
Bevacizumab	5	1,162	18.6	***1.8***[d] (1.4, 2.3)	5	8	2,652	1.1	1.9 (0.9, 4.0)	91
Cetuximab	1	74	0.0	1.0 (0.4, 2.4)	∞	1	74	5.4	3.0 (0.3, 27.5)	19
Erlotinib	4	1,545	10.6	***3.2*** (1.3, 7.7)	9	4	1,545	0.7	3.8 (0.6, 21.8)	143
Gefitinib—all studies	8	5,344	2.0	1.1 (0.8, 1.7)	50	8	5,901	−0.1	0.9 (0.3, 2.8)	−1,000
Gefitinib—parallel analysis[a]	2	1,726	2.3	1.6 (1.0, 2.5)	43	2	2,283	0.2	2.3 (0.4, 14.0)	500
Imatinib—all studies	2	1,766	−9.1	***0.2*** (0.1, 0.4)	−11	2	1,766	−3.1	<***0.01*** (0.0, 0.5)	−32
Imatinib—parallel analysis[a]	1	682	No case was reported in the study			1	682	No case was reported in the study		
Rituximab	8	2,910	−2.8	1.0 (0.8, 1.2)	−36	7	1,688	−0.4	0.8 (0.3, 2.2)	−250
Sorafenib—all studies	2	1,092	4.6	***3.3*** (1.6, 6.6)	22	2	1,092	No case was reported in 2 studies		
Sorafenib—parallel analysis[a]	1	903	3.3	***2.9*** (1.3, 6.3)	30	1	903	No case was reported in the study		
Sunitinib—all studies	2	1,039	24.6	***7.7*** (4.7, 12.8)	4	2	1,039	0.9	1.9 (0.6, 5.7)	111
Sunitinib—parallel analysis[a]	1	304	12.9	***7.6*** (1.8, 31.0)	8	1	304	0.0	1.5 (0.1, 37.0)	∞
Trastuzumab	4	1,786	2.0	1.0 (0.9, 1.2)	50	5	2,012	−1.1	0.6 (0.2, 1.4)	−91

No lapatinib study reported oral mucositis

[a] Parallel analyses excluded studies comparing single-agent targeted therapy with chemotherapy

[b] A number >1 means increased risk; a number <1 means decreased risk

[c] A negative number means one additional adverse event of every *x* patients treated in the control regimen

[d] Italicized bold means the risks were statistically significantly different ($p<0.05$)

No significant difference was observed in the risk of high-grade OM between targeted and standard chemotherapy regimens, except in the case of imatinib which showed a significantly lower risk of high-grade OM (RR=0.03, p=0.01) [113]. Three other targeted agents also had lower risks of high-grade OM, but these differences did not reach statistical significance. OM was not reported in any of the three trials involving lapatinib [63–65].

Diarrhea

Forty-nine and 59 trials reported all-grade and high-grade diarrhea, respectively (Table 3). Diarrhea was the most frequently reported side effect among mucosal side effects. Seven targeted agents, bevacizumab, erlotinib, gefitinib, lapatinib, sorafenib, sunitinib, and trastuzumab, were associated with significantly increased risks of all-grade diarrhea compared with standard of care regimens [19, 22–24, 26, 29, 30, 34, 35, 41, 43–51, 53–59, 61–65, 91–94, 97, 102, 105, 114, 115]. The relative risks ranged from 1.1 to 4.1. There was one additional all-grade diarrhea for every three patients treated with lapatinib or sorafenib compared to those treated with conventional regimens. The adjusted risks of all-grade diarrhea were significantly higher in the sunitinib regimen compared to control regimen (RR=4.0, p<0.0001) [114, 115]. There was one additional all-grade diarrhea of every two patients treated with sunitinib compared to those in the control regimen. No significant difference in the risk of all-grade diarrhea was observed between cetuximab and control regimens [37].

Six drugs, cetuximab, erlotinib, gefitinib, lapatinib, sorafenib, and sunitinib, were associated with significantly increased risks of high-grade diarrhea compared with control regimens [36–38, 41–51, 53–61, 63–65, 90–94, 114, 115]. The relative risk for lapatinib can be as high as 5.2. Patients treated with sunitinib are about eight times more likely to develop high-grade diarrhea than those who receive standard of care (p<0.0001) [114, 115]. Bevacizumab was not associated with an increased risk for high-grade diarrhea compared with control regimens [17, 19–25, 27, 29, 30, 32, 35].

Rituximab and imatinib demonstrated lower risks of all-grade and high-grade diarrhea compared with standard regimens, but this difference reached statistical significance only in the case of imatinib (RR=0.7, p=0.03) [68, 71, 72, 78, 79, 81, 109, 113]. There was one additional all-grade diarrhea for every six patients treated with control regimens compared to those treated with imatinib.

As in the case of mucositis, parallel analyses of subsets of studies excluding those examining single-agent targeted therapy versus chemotherapy showed very consistent results when compared with analyses including all studies.

Other toxicities

Other mucosal toxicities, including GI perforation/hemorrhage, esophagitis, gastritis, oral and aphthous ulcers, and xerostomia, were reported rarely. Three and nine trials of bevacizumab reported all-grade and high-grade GI perforation/hemorrhage, respectively [18, 19, 21, 22, 25, 27, 28, 31–33]. Two erlotinib trials and one sorafenib trial reported high-grade GI perforation/hemorrhage [42, 44, 90]. No statistically significant difference in risk of GI perforation was reported for any agent, although the power to detect differences in risk of such rare events may have been lacking, even in meta-analysis.

Only one trastuzumab trial reported esophagitis; no difference in risk was observed between trastuzumab and control arm [99]. One imatinib trial and one sunitinib trial reported all-grade and high-grade gastritis and two gefitinib trials reported all-grade gastritis [54, 62, 113, 115]. The overall adjusted risks of all-grade gastritis for imatinib and sunitinib regimens were significantly higher than those of control regimens (imatinib—RR=1.8, p=0.001; sunitinib—RR=9.1, p<0.0001). One imatinib trial reported both all-grade and high-grade xerostomia [99]; the RR of xerostomia among patients treated with imatinib was significantly lower than those who received standard chemotherapy (RR=0.2, p<0.0001). Two sunitinib trials reported both all-grade and high-grade xerostomia [114, 115]. The overall adjusted risk for sunitinib regimens of all-grade xerostomia was statistically significantly higher than that of control regimens (RR=2.1, p=0.002). No study reported a case of oral and aphthous ulcers.

Discussion

Our analysis shows that OM, gastritis, esophagitis, and xerostomia are occasional complications of therapy with the targeted agents that we studied, but these problems are not significantly more common or more serious than those observed with standard of care regimens. In contrast, diarrhea is a hallmark of therapy with several of these targeted agents, increasing the risk 2–8-fold compared with conventional regimens. An additional patient with diarrhea will be observed for every three to five patients treated with these targeted agents. Our results are consistent with prior reviews and case series on the topic. Keefe et al. indicated that diarrhea is a common side effect of targeted therapy and can cause severe diarrhea when these targeted drugs are used with chemotherapy [4]. Harandi et al. also pointed out that diarrhea is strongly associated with the use of anti-epidermal growth factor receptor tyrosine kinase inhibitors [117]. Other studies mentioned diarrhea as a common side effect as well [118, 119]. Our analysis showed most of

Table 3 Relative risk of all-grade and high-grade diarrhea among patients receiving targeted therapy drugs

Drug	All-grade diarrhea					High-grade diarrhea				
	No. of studies	No. of patients	Adjusted risk difference estimates (%)	Relative risk (95 % CI)[b]	No. needed to harm (NNH)[c]	No. of studies	No. of patients	Adjusted risk difference estimate (%)	Relative risk (95 % CI)	No. needed to harm (NNH)
Bevacizumab	9	1,745	4.8	***1.1***[d] (1.0, 1.2)	21	13	5,292	1.8	1.1 (0.9, 1.3)	56
Cetuximab	1	74	−2.7	1.0 (0.6, 1.4)	−37	3	1,614	4.7	***1.4*** (1.1, 1.9)	21
Erlotinib	5	2,704	23.6	***2.2*** (1.5, 3.2)	4	6	3,121	5.8	***3.6*** (2.3, 5.6)	17
Gefitinib—all studies	14	8,189	19.2	***2.0*** (1.6, 2.4)	5	15	8,746	3.1	***2.0*** (1.3, 3.3)	32
Gefitinib—parallel analysis[a]	5	4,027	28.7	***2.4*** (2.2, 2.8)	3	5	4,584	5.5	***2.6*** (1.3, 5.3)	18
Imatinib—all studies	2	1,766	−17.7	***0.7*** (0.4, 1.0)	−6	2	1,766	−0.1	1.0 (0.3, 3.3)	−1,000
Imatinib—parallel analysis[a]	1	682	−26.9	***0.5*** (0.4, 0.6)	−4	1	682	1.4	2.0 (0.7, 5.7)	71
Lapatinib	3	2,246	34.3	***2.3*** (1.5, 3.5)	3	3	2,246	8.8	***5.2*** (1.2, 22.6)	11
Rituximab	6	1,326	−4.0	0.9 (0.7, 1.2)	−25	6	1,249	−0.6	0.7 (0.3, 1.6)	−167
Sorafenib—all studies	4	1,915	34.0	***4.1*** (3.4, 5.0)	3	5	2,011	4.2	***3.3*** (1.9, 5.9)	24
Sorafenib—parallel analysis[a]	3	1,726	32.9	***4.1*** (3.3, 5.1)	3	4	1,822	4.1	***3.1*** (1.7, 5.7)	24
Sunitinib—all studies	2	1,039	43.1	***4.0*** (3.2, 5.1)	2	2	1,039	7.4	***8.1*** (3.0, 21.3)	14
Sunitinib—parallel analysis[a]	1	304	21.4	***3.7*** (1.9, 7.5)	5	1	304	3.0	7.6 (0.4, 132.0)	33
Trastuzumab	3	778	12.9	***1.4*** (1.2, 1.7)	8	4	1,004	0.1	0.8 (0.3, 1.9)	1000

[a] Parallel analyses excluded studies comparing single-agent targeted therapy with chemotherapy

[b] A number >1 means increased risk; a number <1 means decreased risk

[c] A negative number means one additional adverse event of every *x* patients treated in the control regimen

[d] Italicized bold means the risks were statistically significant different ($p<0.05$)

the targeted agents studied were associated with significantly higher risks of developing either all-grade or high-grade diarrhea than the conventional regimens. Patients treated with erlotinib, gefitinib, lapatinib, sorafenib, and sunitinib have significantly higher risk of having both all-grade and high-grade diarrhea than those in the conventional regimens, and the risk can be as high as 8-fold for patients treated with lapatinib. The mechanisms underlying diarrhea caused by targeted therapies have been less studied than those occurring with chemotherapy and research is needed in this field.

Ascertaining risk of complications from clinical trials of cancer therapy

Because studies designed to measure the risk of complications are lacking, we used data from anti-neoplastic therapy trials to conduct our meta-analyses. This strategy is known to be associated with underreporting of mucosal toxicities because these problems occur between cycles when monitoring is infrequent [1, 2, 120, 121]. Furthermore, clinical trials rarely include patient reports of mucositis which leads to significant underreporting of complications [122]. Because we report only risk differences and relative risks, which should not be affected by underreporting, we believe our results are accurate. We know of no reasons that mucosal toxicity associated with targeted agents would be either more or less commonly reported than that associated with conventional therapy in the same randomized trial. Unfortunately, however, this situation compromises our ability to comment on the absolute risks of mucosal toxicity and, thus, the magnitude of the problem. (A relative risk of 2.0 describes the difference between rates of 4 % and 2 % as well as the difference between rates of 90 % and 45 %.) Studies of toxicities incorporating patient-reported symptoms and frequent monitoring between cycles are needed to complete our picture of the risk of mucosal toxicities.

Our analysis is further limited in that its results apply only to the targeted agents studied. As can be seen from our analyses, the results varied in important ways among the different targeted agents studied and there are several other agents available that we have not studied.

Fast-track approval of breakthrough agents

Our analyses were limited by the small number of randomized clinical trials of some agents, a result, we believe, of fast-track approval of these promising agents (Table 4). Imatinib was approved in 2001, and there were only two randomized controlled trials that qualified for our review. Cetuximab and erlotinib were examined in four and six qualified studies, respectively.

Table 4 Fast-track approval targeted therapy drugs

Targeted therapy drugs (brand name)	Approval date	No. of studies
Bevacizumab (Avastin)	2/26/2004	20[a]
Cetuximab (Erbitux)	2/12/2004	4
Erlotinib hydrochloride (Tarceva)	11/18/2004	6
Gefitinib (Iressa)	5/5/2003	15
Imatinib (Gleevec)	5/10/2001	2
Lapatinib (Tykerb)	3/13/2007	3
Sorafenib tosylate (Nexavar)	12/20/2005	5
Trastuzumab (Herceptin)	9/25/1998	10

[a] Colorectal cancer indication, 12 trials; breast cancer indication, four trials; non-small cell lung cancer indication, four trials

Expedited approval processes were developed in the early 1990s and codified under the FDA Modernization Act in 1997 [123, 124]. They are critical to the rapid development and delivery of breakthrough drugs for potentially fatal illnesses for which other therapies are lacking. Among the provisions of the Act are mechanisms for provisional approval of an agent based on a single, uncontrolled trial if benefit is shown for a serious or life-threatening illness, provided post-marketing phase IV trials are conducted to confirm the original findings. Despite the benefits enjoyed by many patients, this process has the negative effect of providing little information about side effects, particularly those that are relatively rare. For example, seven early bevacizumab trials reported a total of eight cases of GI perforation that were fatal. Although the risk of death in the bevacizumab regimens was not significantly higher than the conventional regimens, this rare adverse event accounted for a large proportion of deaths in the early trials. In addition to the limited information provided by phase II–III trials of fast-track drugs, in many cases, phase IV, post-marketing studies have been slow to develop and often fail to include comparison groups [125]. Thus, the number of patients treated with targeted agents is insufficient to derive accurate estimates of incidence of rare side effects, even when trials are combined in meta-analysis.

We conclude by emphasizing three points. First, targeted agents that we studied are not associated with clinically significant increases in the risk or severity of most mucosal toxicities. The significantly increased risk of diarrhea is the notable exception to this rule. Second, the absolute incidence of mucosal toxicities with these targeted agents remains unclear because data derived from clinical trials are subject to severe underreporting. Finally, additional information from post-marketing studies is needed to estimate the risks of rare events with sufficient power and precision.

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