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REVIEW ARTICLE

Meta-analysis of cardiovascular toxicity risks in cancer patients on selected targeted agents

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Abstract
Purpose The purpose was to estimate the risk and severity of cardiovascular toxicities associated with selected targeted agents.
Methods We searched English-language literature for randomized clinical trials published between January 1, 2000 and November 30, 2013 of targeted cancer therapy drugs approved by the FDA by November 2010. One hundred ten studies were eligible. Using meta-analytic methods, we calculated the relative risks of several cardiovascular toxicities [congestive heart failure (CHF), decreased left ventricular ejection fraction (DLVEF), myocardial infarction (MI), arrhythmia, and hypertension (HTN)], adjusting for sample size using the inverse-variance technique. For each targeted agent and side effect, we calculated the number needed to harm. Results: Regarding CHF, trastuzumab showed significantly greater risk of all-grade and high-grade CHF. There was significant increased risk of all-grade DLVEF with sorafenib, sunitinib, and trastuzumab and high-grade DLVEF with bevacizumab and trastuzumab. Sorafenib was associated with significant increased all-grade risk of MI based on one study. None was associated with high-grade risk of MI or increased risk of arrhythmia. Bevacizumab, sorafenib, and sunitinib had significant increased risk of all-grade and high-grade HTN.
Conclusions Several of the targeted agents were significantly associated with increased risk of specific cardiovascular toxicities, CHF, DLVEF, and HTN. Several had significant increased risk for high-grade cardiovascular toxicities (CHF, DLVEF, and HTN). Patients receiving such therapy should be closely monitored for these toxicities and early and aggressive treatment should occur. However, clinical experience has demonstrated that some of these toxicities may be reversible and due to secondary effects.

Keywords Cardiovascular toxicity · Targeted agent · Congestive heart failure · Decreased left ventricular ejection fraction · Myocardial infarction · Hypertension

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Introduction

One of the most significant complications of cancer therapy is cardiovascular toxicity [1, 2]. This has become especially relevant as newer cancer treatments are developed and are associated with standard treatment or are rapidly becoming alternatives for traditional chemotherapy regimens. As these targeted agents, including monoclonal antibodies and small molecular multi-targeted therapeutic agents, have been utilized more frequently

in a spectrum of both hematological and solid tumors, cardiovascular toxicities have been noted. Specific cardiovascular toxicities include congestive heart failure (CHF), decreased left ventricular ejection fraction (DLVEF), myocardial infarction (MI), arrhythmia, and hypertension (HTN) [1, 3]. Because of these toxicities, delays or discontinuation of cancer treatment and subsequent worsening of cancer outcomes and quality of life may occur. Additionally, they often increase cost of care and utilization of healthcare resources. Therefore, it is important to estimate the risk and severity of cardiovascular toxicities when targeted agents are utilized.

Because of issues in estimating incidence of cardiac adverse effects, the increasing growth in development and clinical usage of these therapies, the small sample sizes sometimes noted in clinical trials with some of these agents, and the impact they may have on the health of the patient, it is imperative that a better understanding of the risks and severity of these various cardiovascular toxicities is examined. Therefore, the objective of this study was to perform a meta-analysis of clinical trials of Food and Drug Administration (FDA)-approved targeted agents to estimate their incremental risks and severity of various cardiovascular toxicities, including CHF, DLVEF, MI, arrhythmia, and HTN [2, 4].

Patients and methods

Search strategy

We identified 110 English-language randomized trials of 26 targeted cancer therapy drugs approved by the FDA as of November 2010 that had been published between January 1, 2000 and November 30, 2013 in MEDLINE [5]. We expanded our original inclusion dates during our analysis so that we could include as many agents as possible; however, because of the rapid approval cycle for some, more targeted agents were approved after our analysis was complete. In addition, we tried to base our meta-analysis on as many studies available; some agents were fast tracked for approval with only a few papers available. Appendix lists the 26 approved drugs and indications. Although gefitinib was withdrawn from the market in the USA on April 25, 2012 [6], it is used in the European Union [7]. Therefore, it was included in the analysis. Phase II or III randomized control trials, drug names (brand or generic) and their FDA-approved indications (breast neoplasms, colorectal neoplasms, head and neck neoplasms, non-Hodgkin's lymphoma, non-small-cell lung neoplasms, gastrointestinal stromal tumor, etc.) were the keywords used for the literature search. Only studies reporting the results of trials comparing targeted and standard of care chemotherapy regimens were included for analysis. In most cases, this resulted in a comparison of a standard of care chemotherapy regimen to the same regimen plus a targeted agent. However, in a few cases the standard of care was no therapy (post-adjuvant therapy of breast cancer or renal cell carcinoma). Therefore, the comparison is to placebo or no therapy. Finally, in limited cases, most notably with the agent, gefitinib, the targeted agent alone was compared with chemotherapy. Phase I or Phase I/II dose-findings studies, and studies lacking a control group receiving standard of care regimens or without toxicity data, or those reported results from interim or subset analysis were excluded.

Our search retrieved 2496 potentially relevant articles. After excluding review articles, economic evaluation articles, case reports, commentaries, single-arm trials, and phase I trials, 137 articles were identified for review [8–144]. An additional 29 articles were excluded because they were reports of follow-up or maintenance studies or there were fewer than three studies of a targeted drug [9, 10, 17, 49, 56, 58, 65, 76, 79–81, 93, 95, 97–100, 102, 113, 116, 126–128, 130, 137, 139, 140, 142]. After these exclusions, a total of 108 [8, 11–16, 18–48, 50–55, 57, 59–64, 66–75, 77, 78, 82–92, 94, 96, 101, 103–112, 114, 115, 117–125, 129, 131–136, 138, 143, 144] articles describing trials of nine targeted drugs remained for review (Fig. 1). The targeted drugs included bevacizumab, cetuximab, erlotinib, gefitinib, imatinib, lapatinib, rituximab, sorafenib, and trastuzumab. In retrospect, however, we considered sunitinib of such clinical importance that the two trials of this agent were included in the final analysis [127, 128]. With these additions, a total of 110 articles were included in the review (Fig. 1). The majority of the trials used either the National Cancer Institute Common Toxicity Criteria versions 1, 2, or 3 to assess the severity of side effects, while a few trials used the WHO Toxicity Criteria, National Cancer Institute of Canada Common Toxicity Criteria, or New York Heart Association classification.

Data extraction

Information about trial design (phase II, II-III, or III), regimen, and cardiovascular toxicity for each study were recorded by reviewers. Treatment regimen information included regimen (targeted therapy, chemotherapy, and/or radiotherapy) and total number of patients in each arm. Cardiovascular adverse events were categorized into five groups, including CHF, DLVEF, MI, arrhythmia, and HTN. The toxicity assessment method, assessment frequency, total number of all-grade (1–5) and high-grade (3–5) side effects, number of hospitalizations, and number of deaths also were recorded.

Statistical analysis

Our goal was to estimate the unique contribution of the targeted drug to the risk of cardiovascular side effects. First, the risk of each side effect for each trial was calculated. Overall adjusted risk for each drug was estimated as a weighted average of risk using the inverse-variance method that took into account the weights of all studies. The risk difference between the targeted regimen and the standard of care regimen

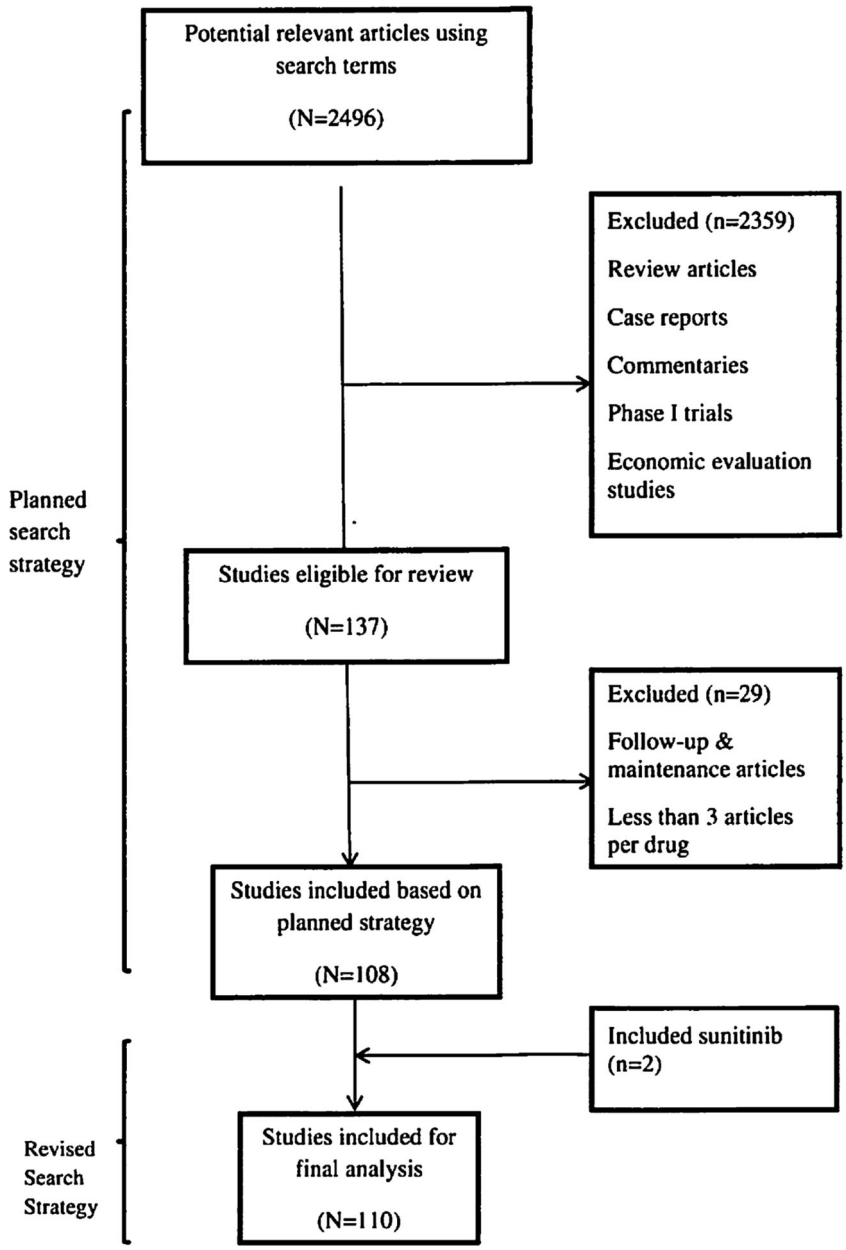

Fig. 1 Flow chart of literature search and trial selection process

was calculated. Finally, the relative risk of cardiovascular side effects for each agent was computed by utilizing a half-integer continuity correction for studies reporting no events in the treatment or control group. The relative risks and 95 % confidence intervals were derived from Comprehensive Meta-Analysis version 2 (CMA). The number needed to harm (NNH), the reciprocal of the adjusted risk increase, was calculated to provide clinically meaningful estimates of the risk of adverse events of targeted drugs [145].

Heterogeneity of the trials was assessed using Cochran's Q statistic. The assumption of homogeneity was considered invalid when the p value is less than 0.1, and a random-effects model was used to derive relative risk and 95 % confidence intervals. Otherwise, results from both fixed-effects and random-effects models were considered. A two-tailed p value of less than 0.05 was deemed to be statistically significant.

As previously mentioned, some standard of care control regimens involved no therapy. 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 cardiovascular complications with targeted plus conventional chemotherapy is multiplicative (rather than additive). We are not aware of any studies 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

Congestive heart failure

Based on analysis of nine trials for all-grade CHF, trastuzumab showed significantly greater risk (RR 5.8) and had a number needed to harm (NNH) of 9. This translates into one additional all-grade CHF compared to those patients in the control regimens for every nine patients treated with trastuzumab. Bevacizumab had a RR of 1.8 and NNH of 71 for all-grade CHF while there were no case reported in the one erlotinib study and no studies of lapatinib or lapatinib-parallel analysis.

With regards to high-grade CHF, nine studies were evaluated. Again, trastuzumab had an increased RR of 5.9; for every 14 patients treated with trastuzumab, there was one additional high-grade CHF compared to those patients in the control regimen. In the one study of erlotinib, there was no case reported. For lapatinib, there was no increased risk of high-grade CHF in the one study evaluated. However, bevacizumab had a RR of 3.5 with a NNH of 71. We conclude that trastuzumab has a significant risk for both all-grade and high-grade CHF in comparison to the other targeted agents studied (Table 1).

Decreased left ventricular ejection fraction

Twenty-two and 19 trials reported all-grade and high-grade DLVEF, respectively (Table 1). The RR of sorafenib (9.4; NNH = 6; based on only one study of 96 patients), sunitinib (4.3; NNH = 11), and trastuzumab (3.0; NNH = 5) were increased. Cetuximab had a significantly lower risk of all-grade DLVEF (RR = 0.1). There was 1 additional all-grade DLVEF for every 25 patients treated with control regimens compared to those treated with cetuximab. No study of erlotinib, gefitinib, or imatinib reported a DLVEF case. Bevacizumab, lapatinib, and rituximab also showed no significant increased risk of all-grade DLVEF.

Trastuzumab had the highest RR (6.7; NNH = 3) of targeted agents for high-grade DLVEF. Bevacizumab also had an increased RR of 3.4 with NNH = 167. There was no significant increase in risk of high-grade DLVEF for lapatinib, sorafinib, and sunitinib. There were no studies to evaluate cetuximab and sorafenib-parallel analysis, and there were no cases of high-grade DLVEF in the three trials utilizing rituximab. We conclude sorafenib, sunitinib, and trastuzumab had significantly increased risk of all-grade DLVEF while bevacizumab and trastuzumab had significantly increased risk for high-grade DLVEF. Further, cetuximab demonstrated a significant lower risk of all-grade DLVEF compared with standard chemotherapy regimens.

Myocardial infarction

Two and 6 trials for all-grade and high-grade MI were evaluated, respectively (Table 2). In all-grade MI, there was one study for sorafenib and one study for sorafenib-parallel analysis. Both showed a RR of 11.0 with a NNH of 22; however, the total number (N = 92) was small and results should be interpreted judiciously. There were no studies of erlotinib, gelfitinib, rituximab, trastuzumab, bevacizumab, cetuximab, imatinib, lapatinib, and sunitinib reporting all-grade MI cases. There was no significant increased risk for high-grade MI among any of the agents. In conclusion, only sorafenib increased all-grade MI; however this finding was based on only one study of 96 patients.

Arrhythmia

Three studies for both all-grade and high-grade arrhythmia were evaluated (Table 2). There were no studies of bevacizumab, cetuximab, erlotinib, gefitinib, imatinib, lapatinib, sorafenib, and sunitinib reporting arrhythmia cases. Neither rituximab nor trastuzumab had an increased risk for all-grade arrhythmia. For high-grade arrhythmia, there were no studies reporting any cases utilizing trastuzumab. The three studies evaluating rituximab for high-grade arrhythmia showed no increased risk. In summary, there was no evidence of increased risk of all-grade or high-grade arrhythmia among any of the agents evaluated.

Hypertension

Based on 35 studies for analysis of all-grade HTN, bevacizumab (RR 5.3; NNH 5), sorafenib-all studies (RR 3.9; NNH 8), sorafenib-parallel analysis (RR 3.6; NNH 9), sunitinib-all studies (RR 7.0; NNH 5), and sunitinib-parallel analysis (RR 5.1; NNH 11) had increased risk (Table 3). Trastuzumab had no studies reporting cases. Similar findings were noted in the 45 studies evaluated for high-grade HTN. Bevacizumab (RR 6.7; NNH 14), sorafenib-all studies (RR 4.4; NNH 20), sorafenib-parallel analysis (RR 5.0; NNH 19), sunitinib-all studies (RR 10.3, NNH 11), and sunitinib-parallel analysis (RR 8.4, 143) all had increased risk for high-grade HTN. We conclude that bevacizumab, sorafenib, and sunitinib have significantly increased risks for both all-grade and high-grade HTN. In addition, parallel analyses of subsets of studies with sorafenib and sunitinib excluding those examining single-agent targeted therapy versus chemotherapy showed very consistent results when compared with analyses including all studies. Figure 2 notes the relative risks of cardiovascular toxicities.

Table 1 Relative risk of all-grade and high-grade congestive heart failure (CHF) and decreased left ventricular ejection fraction (DLVEF) among patients receiving targeted therapy drugs

Drug[a]	No. of studies	No. of patients	Adjusted risk difference estimates (%)	Relative risk (95 % CI)[b]	No. needed to harm (NNH)[c]	Heterogeneity *p* value[e]	Egger's test *p* value[f]	No. of studies	No. of patients	Adjusted risk difference estimate (%)	Relative risk (95 % CI)[b]	No. needed to harm (NNH)[c]	Heterogeneity *P* value[e]	Egger's test *p* value[f]
	All-grade CHF							High-grade CHF						
Bevacizumab	3	843	1.4	1.8 (0.5, 7.2)	71	0.25	0.60	4	3276	1.4	3.5 (1.0, 12.3)	71	0.09	0.87
Erlotinib	1	113	No CHF case was reported in the study			–	–	1	113	No CHF case was reported in the study				
Lapatinib	0	0	Only high-grade CHF reported			–	–	1	443	−0.2	0.3 (0.0, 8.1)	455	N/A	N/A
Lapatinib—parallel analysis*	0	0	Only high-grade CHF reported			–	–	1	443	−0.2	0.3 (0.0, 8.1)	455	N/A	N/A
Trastuzumab	5	7074	11.2	*5.8*[d] (3.6, 9.3)	9	0.39	0.46	2	3865	7.1	*5.9* (2.5, 14.0)	14	0.35	N/A
	All-grade DLVEF							High-grade DLVEF						
Bevacizumab	4	5161	1.8	1.9 (0.9, 4.0)	56	0.03	0.17	6	7256	0.6	*3.4* (1.6, 7.2)	167	0.99	0.95
Cetuximab	1	295	−4.0	*0.1* (0.0, 0.9)	−25	N/A	N/A	0	0	No study reported a high-grade DLVEF case			–	–
Lapatinib	3	2246	0.5	1.5 (0.7, 3.4)	200	0.56	0.01	3	1411	2.0	2.1 (0.9, 4.9)	50	0.25	0.91
Rituximab	3	469	−4.1	0.2 (0.0, 1.4)	−24	0.88	1.00	3	469	No study reported a high-grade DLVEF case			–	–
Sorafenib—all studies	1	96	17.1	*9.4* (1.2, 71.2)	6	N/A	N/A	1	96	1.4	3.1 (0.1, 74.8)	71	N/A	N/A
Sorafenib—parallel analysis*	0	0	No study reported a DLVEF case			–	–	0	0	No study reported a DLVEF case			–	–
Sunitinib—all studies	2	1077	9.4	*4.3* (2.4, 7.7)	11	0.99	N/A	2	1077	1.7	2.6 (0.9, 7.6)	59	0.98	N/A
Sunitinib—parallel analysis*	1	342	5.7	4.3 (1.0, 18.1)	18	N/A	N/A	1	342	0.5	2.5 (0.1, 51.9)	200	N/A	N/A
Trastuzumab	6	5393	19.2	*3.0* (1.3, 6.9)	5	<.01	0.65	3	1764	31.5	*6.7* (4.9, 9.2)	3	0.48	0.54

N/A not available

*Parallel analyses excluded studies comparing single-agent targeted therapy with chemotherapy

[a] No study of erlotinib, gefitinib, imatinib reported decreased LVEF case. No study of cetuximab, gefitinib, imatinib, rituximab, sorafenib, and sunitinib reported CHF case

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

[c] A positive number means one additional adverse event will be observed for every *x* number of patients treated with the targeted regimen; a negative number means one additional adverse event for every *x* number of patients treated with the control regimen

[d] Italicized numbers indicate that the risks were statistically significantly different ($p < 0.05$)

[e] A p value ≥ 0.05 means that the direction and size of risks were consistent across the studies reviewed; $p < 0.05$ means that the risk estimate for one or more studies differed from the reported average risk in either direction or size of risk

[f] A p value ≥ 0.05 means that the observed risk is unlikely to have resulted from publication bias caused by small, low-precision studies with large effect sizes; $p < 0.05$ means that the observed results could have been affected by small, low-precision studies with large effect sizes

Table 2 Relative risk of all-grade and high-grade myocardial infarction (MI) and arrhythmia among patients receiving targeted therapy drugs

Drug[a]	No. of studies	No. of patients	Adjusted risk difference estimates (%)	Relative risk (95 % CI)[b]	No needed to harm (NNH)[c]	Heterogeneity p value[e]	Egger's test p value[f]	No. of studies	No. of patients	Adjusted risk difference estimate (%)	Relative risk (95 % CI)[b]	No. needed to harm (NNH)[c]	Heterogeneity p value[e]	Egger's test p value[f]
	All-grade MI							High-grade MI						
Erlotinib	0	0	Only high-grade MI reported			–	–	1	1159	−0.1	0.3 (0.0, 8.2)	−1156	N/A	N/A
Gefitinib—all studies	0	0	Only high-grade MI reported			–	–	1	141	−0.6	0.4 (0.0, 8.6)	−158	N/A	N/A
Gefitinib—parallel analysis*	0	0	No study reported an MI case			–	–	0	0	No study reported an MI case			–	–
Rituximab	0	0	Only high-grade MI reported			–	–	1	807	−0.4	0.2 (0.0, 4.1)	−250	N/A	N/A
Sorafenib—all studies	1	903	4.5	*11.0*[d] (2.6, 46.4)	22	N/A	N/A	1	96	3.5	5.2 (0.3, 105.7)	29	N/A	N/A
Sorafenib—parallel analysis*	1	903	4.5	*11.0* (2.6, 46.4)	22	N/A	N/A	0	0	No study reported a high-grade MI case			–	–
Trastuzumab	0	0	Only high-grade MI reported			–	–	2	3167	−0.1	0.2 (0.0, 2.3)	−840	0.80	N/A
	All-grade arrhythmia							High-grade arrhythmia						
Rituximab	2	497	3.3	1.7 (0.8, 3.7)	30	0.08	N/A	3	1719	1.3	1.5 (0.9, 2.5)	77	0.50	0.58
Trastuzumab	1	228	0.0	1.0 (0.3, 3.8)	−161,290	N/A	N/A	0	0	Only low-grade arrhythmia reported			–	–

N/A not available

*Parallel analyses excluded studies comparing single-agent targeted therapy with chemotherapy

[a] No study of bevacizumab, cetuximab, erlotinib, imatinib, lapatinib, and sunitinib reported an MI case. No study of bevaxizumab, cetuximab, gefitinib, imatinib, lapatinib, sorafenib, and sunitinib reported an arrhythmia case

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

[c] A positive number means one additional adverse event will be observed for every x number of patients treated with the targeted regimen; a negative number means one additional adverse event for every x number of patients treated with the control regimen

[d] Italicized numbers indicate that the risks were statistically significantly different ($p < 0.05$)

[e] A p value ≥ 0.05 means that the direction and size of risks were consistent across the studies reviewed; $p < 0.05$ means that the risk estimate for one or more studies differed from the reported average risk in either direction or size of risk

[f] A p value ≥ 0.05 means that the observed risk is unlikely to have resulted from publication bias caused by small, low-precision studies with large effect sizes; $p < 0.05$ means that the observed results could have been affected by small, low-precision studies with large effect sizes

Table 3 Relative risk of all-grade and high-grade hypertension (HTN) among patients receiving targeted therapy drugs

Drug[a]	All-grade hypertension							High-grade hypertension						
	No. of studies	No. of patients	Adjusted risk difference estimates (%)	Relative risk (95 % CI)[b]	No. needed to harm (NNH)[c]	Heterogeneity p value[e]	Egger's test p value[f]	No. of studies	No. of patients	Adjusted risk difference estimate (%)	Relative risk (95 % CI)[b]	No. needed to harm (NNH)[c]	Heterogeneity p value[e]	Egger's test p value[f]
Bevacizumab	18	9062	18.4	*5.3*[d] (3.6, 7.7)	5	<0.01	0.06	27	21,440	7.4	*6.7*(4.9, 9.1)	14	0.04	0.42
Sorafenib—all studies	8	2648	12.0	*3.9* (2.0, 7.9)	8	<0.01	0.72	8	2648	4.9	*4.4* (2.1, 9.6)	20	0.15	0.38
Sorafenib—parallel analysis*	6	2363	10.8	*3.6* (1.5, 8.4)	9	<0.01	0.97	6	2363	5.4	*5.0* (2.2, 11.2)	19	0.08	0.51
Sunitinib—all studies	2	1177	22.1	*7.0* (4.4, 11.1)	5	0.44	N/A	2	1177	9.4	*10.3* (4.2, 25.5)	11	0.83	N/A
Sunitinib—parallel analysis*	1	442	9.5	*5.1* (2.0, 12.9)	11	N/A	N/A	1	442	0.7	*8.4* (1.1, 66.1)	143	N/A	N/A
Trastuzumab	0	0	Only high-grade reported case.			–	–	1	3401	0.4	2.0 (0.8, 5.1)	235	N/A	N/A

*Parallel analyses excluded studies comparing single-agent targeted therapy with chemotherapy

N/A not available

[a] No study of cetuximab, erlotinib, gefitinib, imatinib, lapatinib, and trastuzumab reported hypertension case

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

[c] A positive number means one additional adverse event will be observed for every x number of patients treated with the targeted regimen; a negative number means one additional adverse event for every x number of patients treated with the control regimen

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

[e] A p value ≥ 0.05 means that the direction and size of risks were consistent across the studies reviewed; $p < 0.05$ means that the risk estimate for one or more studies differed from the reported average risk in either direction or size of risk

[f] A p value ≥ 0.05 means that the observed risk is unlikely to have resulted from publication bias caused by small, low-precision studies with large effect sizes; $p < 0.05$ means that the observed results could have been affected by small, low-precision studies with large effect sizes

Discussion

Our findings indicate that several of the targeted agents are significantly associated with increased risk of particular cardiovascular toxicities. All-grade risk of cardiovascular toxicities for CHF (trastuzumab), DLVEF (sorafenib, sunitinib, trastuzumab), MI (sorafenib, based on one study of 92 patients), and HTN (bevacizumab, sorafenib, sunitinib) was significantly increased with specific targeted agents. In addition, high-grade risk of cardiovascular toxicities for CHF (trastuzumab), DLVEF (bevacizumab, trastuzumab), and HTN (bevacizumab, sorafenib, sunitinib) was significantly increased with certain targeted agents. Interestingly, the risk of all-grade or high-grade arrhythmia was not demonstrated for any of the studied targeted agents. Further, the all-grade risk of MI was only noted for sorafenib based only on one study with no significant finding of any of the other targeted agents for high-risk of MI. The clinical significance of this finding is unknown.

Heterogeneity and Egger's test were completed. Abnormal findings include the heterogeneity p value (<0.01) (Egger's test was 0.65) for trastuzumab for all-grade DLVEF (Table 1); heterogeneity p values (<0.01) for all-grade HTN included bevacizumab, sorafenib-all studies and parallel analysis; Egger's tests were 0.06, 0.72, and 0.97, respectively. The heterogeneity p value was 0.04 (Egger's test was 0.42) for high-grade HTN for bevacizumab (Table 3). After reviewing probable studies associated with these findings, there are likely multiple factors associated including some with

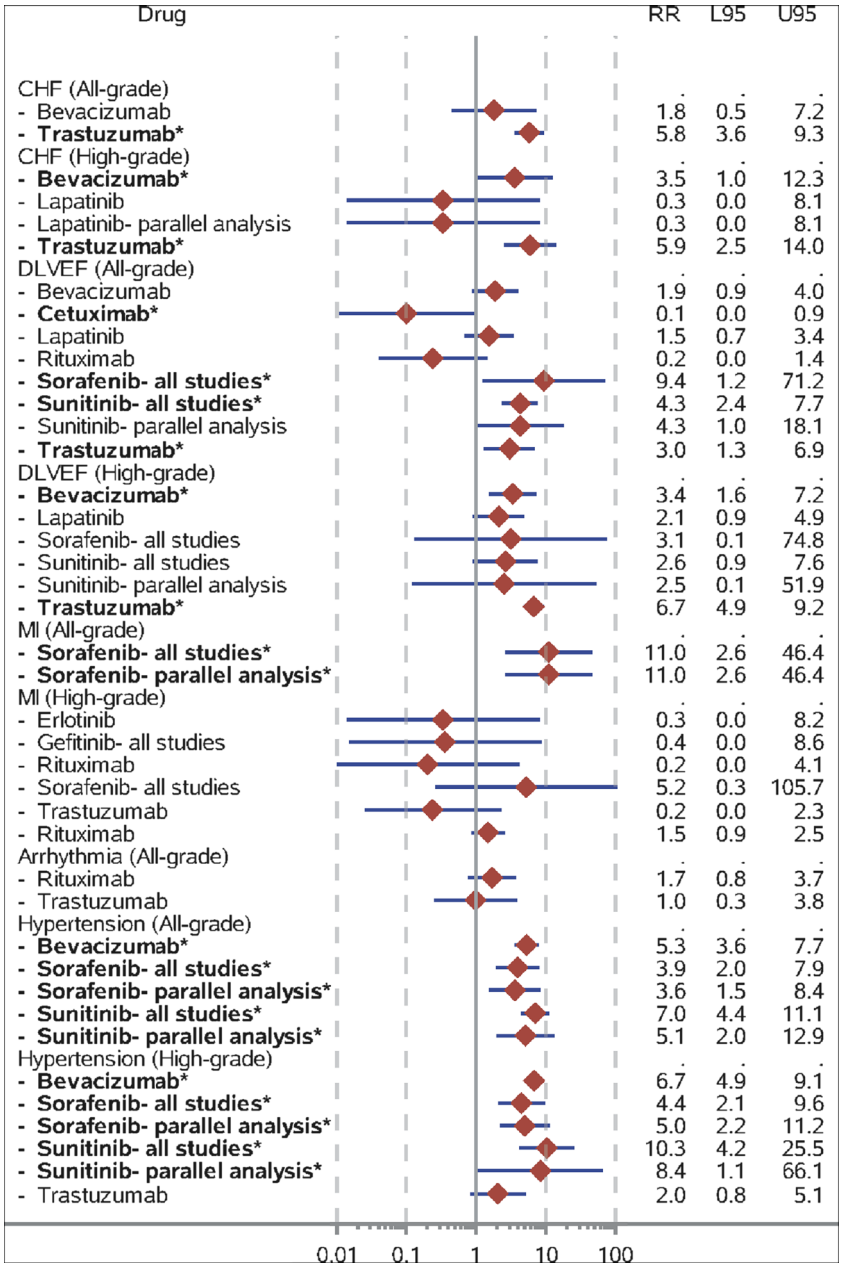

Fig. 2 Relative risks of cardiovascular toxicities and 95 % confidence limits. A relative risk > 1 means risk of toxicity is higher with targeted therapy than with control therapy. A relative risk < 1 means risk of toxicity is lower with targeted therapy than with control therapy. *Asterisks* (*) indicate that relative risk with targeted therapy is significantly higher or lower than the control

smaller sample sizes where it may have been difficult to see the effect and some were earlier studies where the effect may not have been as established and not as readily identified.

The incidence of these toxicities has been difficult to estimate. Many of these therapies are utilized for a short interval during a clinical trial whereas in routine clinical practice, a patient may be on these regimens for months and longer if they are responding to the treatment. In addition, patients with underlying comorbidities, especially those with cardiovascular risk factors, are often excluded from participating in clinical trials utilizing these agents. Further, subclinical cardiac adverse effects may not be noted and thus underestimations of cardiovascular toxicities may occur.

Other reports have noted variation in the incidence and clinical severity of CHF. A recent meta-analysis including almost 7000 patients treated with sunitinib revealed a rate of all-grade tyrosine kinase associated heart failure of 4.1 % [146]. A meta-analysis based on five trials of 1497 patients studying trastuzumab-containing regimens found trastuzumab increased the risk of CHF [RR 3.49, (1.88, 6.47) moderate-quality evidence] and DLVEF [RR 2.65, (1.48, 4.74)] [147]. The findings of our study show a RR of 5.8 (3.6, 9.3) for all-grade and 5.9 (2.5, 14.0) for high-grade CHF, and a RR of 3.0 (1.3, 6.9) for all-grade DLVEF and 6.7 (4.9, 9.2) for high-grade DLVEF. Differences in methodology encompassing studies and agents included may attribute to some variation in results. Funakoshi et al. studied 4878 patients from 13 randomized trials. High-grade HTN had a RR of 3.20 (2.19–4.68) compared to a RR of 4.4 (2.1, 9.6) for high-grade HTN in our study [148]. Another meta-analysis focusing on sorafenib noted a significantly increased risk of hypertension [RR 2.93; (1.52, 5.66); based on 16 studies] and DLVEF [RR 9.38; (1.24, 71.22); based on two studies]. Our findings for sorafenib showed a RR of 3.9 [(2.0, 7.9); based on eight studies] and a RR of DLVEF of 9.4 [(1.2, 71.2); based on one study] [149].

One study limitation is that only available agents approved by the FDA at the time of initiation were included. Since, more agents of this type have been approved by the FDA and are in use. However, we cannot infer from this study that they have similar risk to the agents we studied; for instance the risk of QT interval prolongation with vandetanib led the FDA in 2011 to implement a risk evaluation mitigation strategy program [150]. Another study limitation was that some agents had very few clinical trials performed prior to their FDA approval due to fast-tracking. This causes difficulty in assessing outcomes via meta-analysis when there are very few studies to base the results upon. For example, although sunitinib had only two studies during our review phase, it was included due to its significant use in clinical practice.

A third study limitation is that our findings were based on clinical trials adhering to strict inclusion/exclusion criteria and treatment algorithms. As these agents have been approved and released by the FDA, routine clinical practice may not include similar populations or adhere to regimented dosing criteria as performed in the clinical trials. Therefore, it may also be noted that documented cardiac events may differ in incidence and severity than those our meta-analysis is based upon.

Some of the endpoints noted may be a secondary endpoint rather than a primary endpoint. For example, targeted agent induced HTN may lead to myocardial ischemia and infarct rather than the agent directly attributing to the ischemic event [2]. We are not able to specifically determine whether some of the cardiovascular toxicities reported in the various studies are primary or secondary endpoints. However, if they are secondary endpoints, early identification and aggressive treatment of the primary endpoint, such as HTN, may limit or avoid a more significant secondary complication such as MI or CHF.

Recently, clinical experience in the use of some agents, such as trastuzimab, has demonstrated reversibility of CHF. In fact, many breast cancer patients have been rechallenged with trastuzimab following a DLVEF or CHF and have been able to continue on this targeted therapy for several years without recurrence of the toxicity [2]. We must always consider the risk/benefit ratio of utilizing cancer therapies such as these. Particularly in the setting of malignancy, close consideration should be made as to where the benefits of disease control justify the potential cardiovascular toxicities.

In conclusion, although targeted agents may be extremely beneficial in treating various malignancies, there are several with potential cardiovascular toxicities. Clinical experience has demonstrated that some may be transient and reversible and a careful risk/benefit analysis should be undertaken. These targeted therapies may be life-saving for the cancer population. Therefore, we recommend avid education for providers, patients and their families. Patients should be carefully screened prior to administration of agents with these possible effects and should be medically optimized prior to initiating treatment, especially those with significant cardiac disease. For example, patients should have normotensive blood pressure readings prior to initiation of targeted therapies with documented HTN toxicity. And, we promote frequent monitoring of patients on targeted therapies with known cardiovascular toxicity while on active treatment and post-treatment until the targeted therapy no longer may affect the cardiac status. This may allow patients the full benefit of these drugs in fighting their malignancy while potentially preventing cardiovascular complications. Finally, as noted in our results, not all cardiovascular toxicities are equal. Arrhythmia was not a toxicity of the targeted therapies studied and MI was noted as all-grade toxicity for only one of the drugs studied and based on a single small study so that this result should be interpreted judiciously. While CHF, DLVEF, and HTN were noted as all-grade and high-grade toxicities among several of the drugs. In addition, some of these toxicities may not be primary but a secondary toxicity. Further studies are necessary as newer agents in this class are approved and become common in the armamentarium of cancer treatment.

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Compliance with ethical standards

Conflict of interest I have no financial relationship with any organization that sponsored the research. I have full control of all primary data and will allow the journal to review the data if requested.

Appendix

Table 4 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, mantel call 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

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

*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

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