Title
Association between treatment toxicity and outcomes in oncology clinical trials

Journal
Annals of Oncology, 25(11)

ISSN
0923-7534

Authors
Abola, MV
Prasad, V
Jena, AB

Publication Date
2014-11-01

DOI
10.1093/annonc/mdu444

Peer reviewed

15. Hamid O, Schmidt H, Nissan A et al. A prospective phase II trial exploring the association between tumor microenvironment biomarkers and clinical activity of ipilimumab in advanced melanoma. J Transl Med 2011; 9: 204.
16. Hersh EM, O'Day SJ, Powderly J et al. A phase II multicenter study of ipilimumab with or without dacarbazine in chemotherapy-naïve patients with advanced melanoma. Invest New Drugs 2011; 29: 489–498.
17. Chiarion-Sileni V, Pigozzo J, Ascierto PA et al. Ipilimumab retreatment in patients with pretreated advanced melanoma: the expanded access programme in Italy. Br J Cancer 2014; 110: 1721–1726.
18. Schadendorf D, Hodi FS, Robert C et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in metastatic or locally advanced, unresectable melanoma. In Presented at the European Cancer Congress 2013, 27 September–1 October 2013 (Abstr 24LBA). Amsterdam, The Netherlands 2013.
19. Robert C, Schadendorf D, Messina M et al. MDX010-20 investigators. Efficacy and safety of retreatment with ipilimumab in patients with pretreated advanced melanoma who progressed after initially achieving disease control. Clin Cancer Res 2013; 19: 2232–2239.
20. Ibrahim RA, Berman DM, DePril V et al. Ipilimumab safety profile: summary of findings from completed trials in advanced melanoma. J Clin Oncol 2011; 29: Abstr 8583.
21. YERVOY™ (ipilimumab) US Prescribing Information: Risk Evaluation and Mitigation Strategy. Bristol-Myers Squibb Company; 2011; http://www.yervoy.com/hcp/rems.aspx (June 2014, date last accessed).
22. Weber JS, Kähler KC, Hauschild A. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol 2012; 30: 2691–2697.
23. Feng Y, Roy A, Masson E et al. Exposure-response relationships of the efficacy and safety of ipilimumab in patients with advanced melanoma. Clin Cancer Res 2013; 19: 3977–3986.

Annals of Oncology 25: 2284–2289, 2014
doi:10.1093/annonc/mdu444
Published online 5 September 2014

Association between treatment toxicity and outcomes in oncology clinical trials

M. V. Abola[1], V. Prasad[2] & A. B. Jena[3,4]*

[1]*Department of Family Medicine, Case Western Reserve University School of Medicine, Cleveland;* [2]*Medical Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda;* [3]*Department of Health Care Policy, Harvard Medical School, Boston;* [4]*Department of Medicine, Massachusetts General Hospital, Boston, USA*

Received 4 July 2014; revised 18 August 2014; accepted 20 August 2014

Background: Whether or not toxicity predicts clinical outcomes has long been a question regarding cancer treatments. While prior studies have focused on specific cancers, therapies, and toxicities, no comprehensive evidence exists on whether treatment toxicity predicts favorable outcomes.

Methods: We abstracted treatment toxicity and clinical outcome data from a sample of phase III oncology randomized clinical trials ($n = 99$ trials). We investigated whether treatments with relatively greater toxicity compared with their controls had relatively higher, lower, or equivocal rates of clinical efficacy, measured by progression-free survival (PFS) and overall survival (OS). Several toxicities were assessed (all grades, grades III/IV, cutaneous rash, gastrointestinal toxicity, and myelosuppression).

Results: Toxicity and efficacy were greater among treatments than controls (e.g. 3.5 instances of all-grade toxicity per patient in treatment arms versus 2.8 instances in controls, $P < 0.001$; mean PFS of 9.1 months across treatment arms versus 7.1 months across controls, $P < 0.001$; mean OS of 18.6 months across treatment arms versus 16.9 months across controls, $P < 0.001$). Across trials, greater relative treatment toxicity was strongly associated with greater PFS in treatments versus controls ($P < 0.001$), but not OS ($P = 0.44$). Although higher relative rates of myelosuppression and cutaneous rash among treatments were not associated with greater treatment efficacy, greater relative gastrointestinal toxicity among treatments was associated with greater relative PFS compared with controls ($P = 0.007$).

Conclusion: Across trials, treatments with relatively greater all-grade toxicity compared with controls are associated with relatively greater PFS but not OS.

Key words: treatment toxicity, clinical trials

introduction

Whether or not toxicity of treatment predicts meaningful clinical outcomes has long been a question in cancer medicine, with available evidence offering mixed conclusions. Across a range of cancers, cytotoxic side-effects such as myelosuppression have been linked to improved outcomes in both the adjuvant and metastatic setting [1–6]. For example in an analysis of patients with advanced nonsmall-cell lung cancer treated with cytotoxic agents, both severe and mild neutropenia were associated with improved survival, leading authors to speculate that the absence

Correspondence to: Prof. Anupam B. Jena, Department of Health Care Policy, Harvard Medical School, 180 Longwood Avenue, Boston, MA 02115, USA. Tel: +1-617-432-8322; E-mail: jena@hcp.med.harvard.edu

of myelosuppression may reflect inadequate dosing [5]. In contrast, other studies demonstrate either equivocal or negative associations between rates of treatment-related myelosuppression and clinical outcomes [7, 8]. Aside from myelosuppression, specific toxicities unique to certain agents have also been associated with improved outcomes. For instance, vasomotor symptoms, musculoskeletal adverse events, and vulvovaginal symptoms predict improved outcomes among women taking adjuvant tamoxifen or aromatase inhibitors [9]. Arthralgia, myalgia, and carpal tunnel symptoms have similarly been associated with better disease-free survival in this setting [10]. Peripheral neuropathy is associated with improved outcomes in recurrent ovarian cancer for patients receiving carboplatin–paclitaxel [6], but not for patients with breast cancer receiving adjuvant taxane-containing therapy [11]. Rates of hypertension correlate with efficacy among patients with renal cell cancer on kinase inhibitors [12]. Among patients with advanced colorectal carcinoma, an aggregate score of all chemotherapy-induced toxicities is positively associated with greater treatment efficacy [13].

While prior studies have typically focused on some combination of a specific cancer, adjuvant or metastatic treatment, specific agent, or specific toxicities, to our knowledge no comprehensive evidence exists on whether rates of treatment toxicity in oncology are generally correlated with treatment outcomes. Comprehensively identifying whether higher rates of treatment toxicity predict clinical response to treatment is important for several reasons. First, it addresses a general biological question: in the case of cytotoxic treatments, whether lack of toxicity is a marker for inadequate dose intensity, and for targeted therapies, whether some degree of off-target effects are predictive of efficacy [14]. Second, the presence of a global relationship—positive or negative—may help identify which therapies are likely to successfully transition between phase II and III clinical trials, a transition that has been characterized by high rates of failure [15].

Abstracting treatment toxicity and clinical outcome data from a sample of phase III oncology randomized clinical trials, we investigated whether treatments with relatively greater toxicity compared with their controls had relatively higher, lower, or equivocal rates of clinical efficacy, measured by progression-free survival (PFS) and overall survival (OS).

methods

We extracted treatment toxicity and outcome data from 116 phase III, randomized, controlled clinical trials of cancer medications. Before application of exclusion criteria, our sample included the 53 most highly cited clinical trials and the 63 most recent clinical trials as of 2 February 2013 (see Figure 1 for inclusion/exclusion criteria).

eligible studies

Thompson Reuters Web of Science was used to identify eligible articles. The following search strings were used to identify appropriate articles: phase III, phase 3, clinical trials, randomized controlled trial, randomized clinical trials, randomized clinical trial, randomized controlled trial, and chemotherapy. Search results were further refined to papers classified under 'oncology' under 'research area.' To obtain our sample of highly cited articles, we sorted all trials by citation count and extracted 53 trials with the largest count. For these articles, there was no limitation on publication year. Our sample of the most recent clinical trials was obtained by searching through phase III oncology trials published from January 2012 to December 2012 in reverse chronologic order. We extracted 63 trials with publication dates from March 2012 to December 2012.

One author screened all studies. Articles were excluded if they reported data strictly in hazard ratios, did not provide median months for PFS, time to progression (TTP), or OS, or if trials simply omitted key data such as PFS, OS, TTP, complete response, or partial response. In total, 99 phase III clinical trials, 54 most recent and 45 highly cited, met our inclusion criteria (Figure 1; supplementary Tables S1 and S2, available at *Annals of Oncology* online).

data extraction

For each trial, we extracted information on the intervention(s) tested, median OS and PFS in treatment and control arms (or median TTP when PFS was unreported), and the following treatment toxicity data: mean number of instances per participant in which all-grade toxicity was

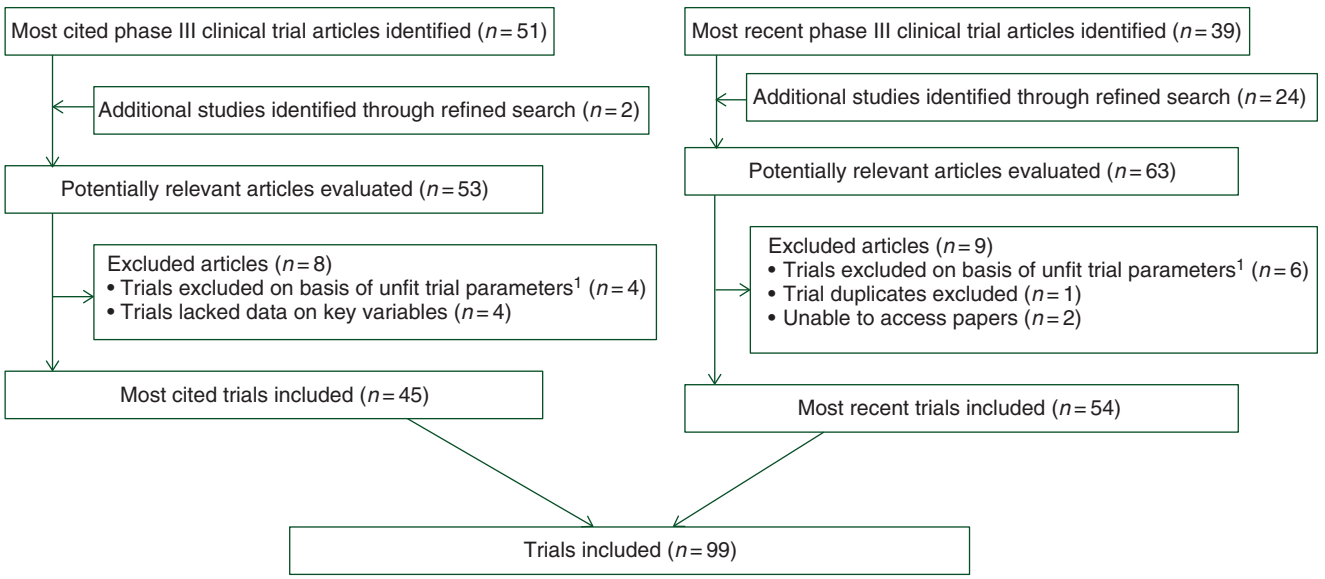

Figure 1. Flow diagram of inclusion of trials.

experienced, grade III–IV toxicity (defined based on the Common Terminology Criteria for Adverse Events guidelines used by primary study authors), myelosuppression, cutaneous rash, or gastrointestinal toxicity. The control arm was defined as the cohort without the investigational agent.

statistical analysis

For both the treatment and control group in each trial, we used data on the mean instances per patient who met a given toxicity end point (e.g. mean instances per patient with all-grade toxicity in the treatment arm and control group) to compute the relative percentage change in toxicity rates between the treatment and control arm. For example in a trial comparing sunitinib versus interferon alfa trial for metastatic renal cell carcinoma [16], there were on average 3.9 instances of all-grade toxicity per patient receiving sunitinib (treatment) compared with 2.6 instances per patient receiving interferon alfa (control), a relative increase of 50%. We similarly computed the percentage increase in median PFS and OS between treatment and control groups in each trial.

Across trials, we estimated univariate associations between the percentage change in treatment toxicity (within a trial) and the percentage change in treatment efficacy (within each trial). In other words, we analyzed whether across trials, those trials in which the treatment was relatively more toxic compared with control were also those trials in which treatment was relatively more efficacious. It is important to compare relative changes in treatment toxicity to relative changes in treatment efficacy within rather than across trials, since the latter approach may be confounded due to differences in cancer mortality across trials (e.g. treatments in trials of patients with pancreatic cancer may be inappropriately compared directly with trials of patients with early-stage breast cancer). This within-trial analysis is statistically similar to regression in which the dependent variable is a given treatment's efficacy and independent variables include the treatment's toxicity rate and an indicator variable for the trial. Our approach used variation in toxicities and efficacies of treatments within trials rather than across trials in order to estimate the association between treatment toxicity and efficacy.

results

Our search generated 116 entries initially considered to be eligible, of which 99 abstracts met eligibility criteria. Table 1 shows the characteristics of the 54 most recent and 45 most highly cited studies that we examined. The median number of citations received by the most highly cited studies was 759. The most highly cited studies included a median of 574 participants, while the most recent studies included a median of 474 patients. Across studies, mean efficacy was higher in treatment than control arms (e.g. mean PFS of 9.1 months across treatment arms versus 7.1 months across control arms, $P < 0.001$; mean OS of 18.6 months across treatment arms versus 16.9 months across control arms, $P < 0.001$). The most highly cited studies were more likely to be positive—i.e. demonstrate clinical efficacy of the treatment arm relative to control—than the most recent studies (88.9% versus 48.1%, $P < 0.001$). Across all studies, mean rates of all-grade or grade III and IV toxicity were also more common in treatment than control arms (e.g. 3.5 instances of all-grade toxicity per patient in treatment arms versus 2.8 instances per patient in control arms, $P < 0.001$; 0.8 instances per patient of grade III/IV toxicity in treatment arms versus 0.6 instances per patient in control arms, $P < 0.001$).

Figure 2 shows the relationship across trials between the relative toxicity of treatment compared with control (computed within a trial) versus the relative efficacy of treatment compared with control (computed within a trial). The figure allows us to assess whether trials in which the relative toxicity of treatment

Table 1. Characteristics of oncology trials

Characteristics of trials	Most cited trials ($n = 45$ trials)	Most recent trials ($n = 54$ trials)	All trials ($n = 99$ trials)
Median no. of citations (IQR)	759 (590–967)	1.5 (0–4.75)	11 (1–720.5)
Median sample size in trial (IQR)	571 (373–792)	474 (248–828)	512 (280–828)
Treatment efficacy			
Mean PFS across treatment arms, months (95% CI)	8.3 (6.0–10.5)	9.5 (7.0–12.0)	9.1 (7.3–10.9)
Mean PFS across control arms, months (95% CI)	5.6 (3.8–7.5)	7.8 (5.9–9.8)	7.1 (5.7–8.5)
Mean OS across treatment arms, months (95% CI)	16.5 (12.6–20.5)	20.3 (14.9–25.6)	18.6 (15.2–21.9)
Mean OS across control arms, months (95% CI)	14.3 (10.9–17.7)	18.9 (13.9–24.1)	16.9 (13.7–20.1)
Percent of trials with positive treatment findings[a]	88.9	48.1	66.7
Toxicities			
Mean instances per patient of all-grade toxicity across treatment arms (95% CI)	3.7 (2.7–4.8)	3.4 (2.6–4.1)	3.5 (2.9–4.2)
Mean instances per patient of all-grade toxicity across control arms (95% CI)	3.2 (2.0–4.4)	2.5 (1.8–3.1)	2.8 (2.2–3.5)
Mean instances per patient of grades III/IV toxicity across treatment arms (95% CI)	0.7 (0.5–0.9)	0.9 (0.7–1.1)	0.8 (0.7–0.9)
Mean instances per patient of grades III/IV toxicity across control arms (95% CI)	0.6 (0.4–0.8)	0.6 (0.4–0.8)	0.6 (0.5–0.7)

[a]Positive trials were defined as those in which the authors declared a statistically significant improvement in outcomes with treatment over control (with outcomes most commonly defined as OS, PFS, or TTP).
PFS, progression-free survival; OS, overall survival.

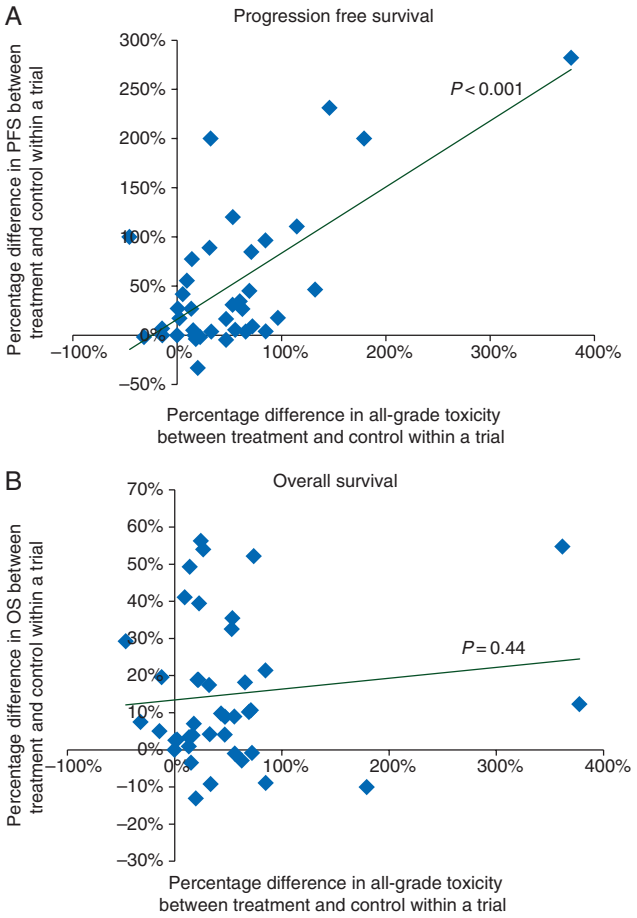

Figure 2. Association between relative treatment toxicity (all grade) and relative treatment efficacy within trials, according to efficacy outcome. Each panel plots the percentage difference in efficacy between treatment and control in a given trial (e.g. PFS in panel A) against the percentage difference in toxicity. Each point in a plot reflects a clinical trial.

compared with control was greater were also trials in which the relative efficacy of treatment compared with control was greater. Across trials, greater relative treatment toxicity was strongly statistically significantly correlated ($P < 0.001$) with greater PFS in treatments versus controls. For example a 10 percentage point increase in relative treatment toxicity (e.g. comparing trials in which treatments were 30% more toxic than controls to trials in which treatments were 40% more toxic) was associated with a 6.7 percentage point increase in relative treatment PFS (e.g. increasing a treatment's relative efficacy from being 20% more effective than control to being 26.7% more effective than control), $P < 0.001$ (Table 2). In contrast, greater relative treatment toxicity was not statistically significantly associated with greater OS in treatments versus controls. A 10 percentage point increase in relative treatment toxicity was associated with a 0.3 percentage point increase in relative treatment OS, $P = 0.44$ (Table 2).

Similar associations held in subgroup analyses of the most highly cited versus most recent trials, which were carried out since the most highly cited trials may be those in which treatments were both more efficacious and less toxic than controls, which would bias us toward finding a negative association between treatment toxicity and efficacy. Specifically, among the most recent trials (which would not suffer from this bias), a 10 percentage point increase in relative treatment toxicity was associated with a 7.0 percentage point increase in relative treatment OS, $P < 0.001$. Among the most highly cited trials, a 10 percentage point increase in relative treatment toxicity was associated with a 6.1 percentage point increase in relative treatment OS, $P < 0.001$.

An analysis of specific types of toxicities (cutaneous rash, gastrointestinal toxicity, or myelosuppression) demonstrated a strong statistically significant association between a treatment's relative gastrointestinal toxicity and its relative PFS compared with control (Table 2). For example, a 10 percentage point increase in a treatment's relative gastrointestinal toxicity was

Table 2. Association between relative treatment toxicity and relative treatment efficacy within trials, according to type of toxicity and efficacy outcome

	Effect of a 10 percentage point increase in relative treatment toxicity on relative treatment efficacy, percentage point change (95% CI)	
Toxicity	Progression-free survival	Overall survival
All-grade toxicity	6.7% (4.2% to 9.2%)	0.3% (−0.5% to 1.1%)
Specific toxicities		
Cutaneous rash	0.2% (−0.7% to 1.1%)	0.2% (−0.2% to 0.6%)
Gastrointestinal toxicity	3.4% (1.0% to 5.7%)	0.2% (−0.5% to 0.9%)
Myelosuppression	0.2% (−2.7% to 2.3%)	0.4% (−1.4% to 0.6%)

The table shows the univariate association across trials between the relative treatment toxicity (computed within a trial) and relative treatment efficacy (also computed within trials). Relative treatment toxicity within a trial is defined as the percentage increase or decrease in toxicity of the treatment arm compared with the control arm. Relative treatment efficacy within a trial is defined as the percentage increase or decrease in efficacy (either PFS or OS) of the treatment arm compared with the control arm. These estimates therefore assess whether trials in which treatments were relatively more toxic compared with controls were also trials in which treatments were relatively more efficacious compared with controls. These estimates imply that across trials, a 10 percentage point increase in relative treatment toxicity (e.g. comparing trials in which treatments were 30% more toxic than controls to trials in which treatments were 40% more toxic) is associated with a 6.7% percentage point increase in relative treatment PFS (e.g. increasing a treatment's relative efficacy from being 20% more effective than control to being 26.7% more effective than control).

associated with a 3.4 percentage point increase in its PFS relative to control, $P = 0.007$ (Table 2). Greater relative rates of myelosuppression and cutaneous rash among treatments compared with controls were not associated with relative differences in PFS or OS for treatments compared with controls.

discussion

The association between treatment toxicity and clinical outcomes is a longstanding issue in cancer medicine [1–9, 11–13]. Using data on treatment toxicity and clinical outcomes obtained from a sample of phase III oncology trials, we examined whether treatments with relatively greater toxicity compared with their controls had higher, lower, or equivocal rates of clinical efficacy. By analyzing treatment toxicity and clinical outcome data across a number of trials, our analysis adds to prior studies that have typically focused on a single combination of specific cancer, adjuvant or metastatic setting, specific agent, and specific toxicities such as cutaneous rash, gastrointestinal toxicity, or myelosuppression.

Our evidence suggests a potentially strong relationship between a treatment's all-grade relative toxicity and its relative PFS compared with alternative therapy. We found no relationship a treatment's all-grade relative toxicity and its relative OS compared with alternative therapy. An analysis of specific toxicities demonstrated a strong association between a treatment's relative gastrointestinal toxicity and its relative PFS, but no association between relative efficacy and rates of myelosuppression or cutaneous rash.

A recent trial demonstrates how toxicity can be associated with improved clinical efficacy. The Japanese Gynecologic Oncology Group compared two strategies in the treatment of advanced ovarian cancer: a standard course of paclitaxel and carboplatin, and a dose-dense version of this regimen. The study found that more carboplatin could be administered to the conventionally dosed group, while the mean dose of paclitaxel was higher in the dose-dense group. This dosing pattern was itself a consequence of dose modification due to toxicity, which was greater among the dose-dense group. Patients receiving dose-dense carboplatin–paclitaxel had a higher frequency of grade 3 or 4 anemia (69% versus 44%) [17]. In this case, the dose-dense regimen demonstrated improvements in both PFS (28.0 versus 17.2 months) [17] and OS (100.5 versus 62.2 months) [18]. Our analysis also relates to evidence on the benefit of individualized dose adjustment between chemotherapy cycles, which has shown impressive outcomes in primary mediastinal B-cell lymphoma [19] and, more recently, Burkitt's lymphoma [20]. These individualized regimens use nadir white counts and platelet levels to guide dose escalation in subsequent cycles. In the case of dose-adjusted EPOCH-R, toxicity is explicitly used as a surrogate of efficacy.

The intent of our study was to provide an overall view of the association between treatment toxicity and efficacy using trial-level data, an approach with inherent limitations. First, a more comprehensive approach would involve meta-analysis of individual patient data across multiple trials, inclusive of different cancer types, modalities (cytotoxic therapy, molecularly targeted therapy, immunotherapy, endocrine therapy, and radiation therapy), measured side-effects, and outcomes. Because we analyzed a limited set of data at the trial level, we were unable to identify whether the association between specific treatment toxicities and outcomes varied according to treatment modality (e.g. cytotoxic versus molecularly targeted versus immune therapies, or combinations of these) or specific cancer, both important questions for assessing the clinical applicability of our findings. Second, although we estimated a statistically significant association between a treatment's relative gastrointestinal toxicity and its relative PFS compared with alternate therapy, our analysis was not powered to identify small but potentially statistically significant associations between other treatment toxicities and efficacy within trials. Other studies have found that myelotoxicty correlates with improved outcomes in advanced lung cancer [5], and that rash can predict improved survival for an epidermal growth factor receptor targeted drug [21]. Moreover, our analysis focused on the number of toxicities associated with treatments, and was not powered to analyze how severity of toxicity (e.g. grades I versus IV toxicity), clinical significance (e.g. rash versus systolic heart failure), or biologic relevance (e.g. on- versus off-target toxicity for molecularly targeted therapies) were associated with outcomes. Fourth, our sample of trials included nearly 50% of the most highly cited phase III trials. These trials may be highly cited because the treatments evaluated were not only more efficacious but also had lower rates of toxicity relative to the comparator therapy. This would have led to a negative association between relative treatment toxicity and efficacy within the most highly cited trials. We restricted analyses to the most recent trials, and continued to find that treatment toxicity was positively correlated with relative PFS across trials.

Additionally, our results should not be misinterpreted. We estimated a trial-level, not individual-level, correlation between toxicity and outcomes. As such, we cannot conclude that those patients who experienced greater toxicity within a trial were necessarily those who also benefitted the most. Within a trial, patients with improved PFS may have lower toxicity with treatment, whereas patients with greater toxicity may have lower benefit. If this trial had larger PFS improvements and toxicity rates compared with other trials, a trial-level analysis would spuriously conclude that treatments with greater toxicity have larger PFS improvements, when in fact patients with greater PFS would have lower toxicity in a patient-level analysis. For this reason, our results should not be misinterpreted to justify increased dosing to achieve toxicity. Instead, our results highlight the possibility that drugs that confer greater adverse events may confer improvements in PFS collectively, but patient-level analyses are needed to confirm this hypothesis. Even with patient-level analysis, however, a positive association between treatment toxicity and efficacy may suffer from a length-time bias, if patients with greater PFS receive treatment longer and therefore have more time to experience treatment-related toxicities.

In summary, in a trial-level analysis of phase III oncology clinical trials, we found that treatments with greater relative toxicity (compared with alternative therapies) have relatively greater PFS. This relationship may be of interest to patients in clinical trials for whom some degree of toxicity may be tolerated while efficacy end points are pending, and has implications for research investigating the role of individualized dose-escalating chemotherapy which entails greater side-effects for a given patient but potentially higher efficacy as well.

funding

Support was provided by the Office of the Director, National Institutes of Health (NIH Early Independence Award, 1DP5OD017897-01, ABJ).

disclosure

The authors have declared no conflicts of interest.

references

1. Saarto T, Blomqvist C, Rissanen P et al. Haematological toxicity: a marker of adjuvant chemotherapy efficacy in stage II and III breast cancer. Br J Cancer 1997; 75: 301–305.
2. Poikonen P, Saarto T, Lundin J et al. Leucocyte nadir as a marker for chemotherapy efficacy in node-positive breast cancer treated with adjuvant CMF. Br J Cancer 1999; 80: 1763–1766.
3. Yamanaka T, Matsumoto S, Teramukai S et al. Predictive value of chemotherapy-induced neutropenia for the efficacy of oral fluoropyrimidine S-1 in advanced gastric carcinoma. Br J Cancer 2007; 97: 37–42.
4. Pallis AG, Agelaki S, Kakolyris S et al. Chemotherapy-induced neutropenia as a prognostic factor in patients with advanced non-small cell lung cancer treated with front-line docetaxel-gemcitabine chemotherapy. Lung Cancer 2008; 62: 356–363.
5. Di Maio M, Gridelli C, Gallo C et al. Chemotherapy-induced neutropenia and treatment efficacy in advanced non-small-cell lung cancer: a pooled analysis of three randomised trials. Lancet Oncol 2005; 6: 669–677.
6. Lee CK, Gurney H, Brown C et al. Carboplatin-paclitaxel-induced leukopenia and neuropathy predict progression-free survival in recurrent ovarian cancer. Br J Cancer 2011; 105: 360–365.
7. Koutras AK, Fountzilas G, Dafni U et al. Myelotoxicity as a prognostic factor in patients with advanced breast cancer treated with chemotherapy: a pooled analysis of two randomised trials conducted by the Hellenic Cooperative Oncology Group. Anticancer Res 2008; 28: 2913–2920.
8. Kumpulainen EJ, Hirvikoski PP, Johansson RT. Neutropenia during adjuvant chemotherapy of breast cancer is not a predictor of outcome. Acta Oncol 2009; 48: 1204–1206.
9. Fontein DBY, Seynaeve C, Hadji P et al. Specific adverse events predict survival benefit in patients treated with tamoxifen or aromatase inhibitors: an international tamoxifen exemestane adjuvant multinational trial analysis. J Clin Oncol 2013; 31: 2257–2264.
10. Huober J, Cole BF, Rabaglio M et al. Symptoms of endocrine treatment and outcome in the BIG 1-98 study. Breast Cancer Res Treat 2014; 143: 159–169.
11. Schneider BP, Zhao F, Wang M et al. Neuropathy is not associated with clinical outcomes in patients receiving adjuvant taxane-containing therapy for operable breast cancer. J Clin Oncol 2012; 30: 3051–3057.
12. Rini BI, de La Motte Rouge T, Harzstark AL et al. Five-year survival in patients with cytokine-refractory metastatic renal cell carcinoma treated with axitinib. Clin Genitourin Cancer 2013; 11: 107–114.
13. Schuell B, Gruenberger T, Kornek GV et al. Side effects during chemotherapy predict tumour response in advanced colorectal cancer. Br J Cancer 2005; 93: 744–748.
14. Fojo T. Commentary: novel therapies for cancer: why dirty might be better. Oncologist 2008; 13: 277–283.
15. Cannistra SA. Phase II trials in journal of clinical oncology. J Clin Oncol 2009; 27: 3073–3076.
16. Motzer RJ, Hutson TE, Tomczak P et al. Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med 2007; 356: 115–124.
17. Katsumata N, Yasuda M, Takahashi F et al. Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 2009; 374: 1331–1338.
18. Katsumata N, Yasuda M, Isonishi S et al. Long-term results of dose-dense paclitaxel and carboplatin versus conventional paclitaxel and carboplatin for treatment of advanced epithelial ovarian, fallopian tube, or primary peritoneal cancer (JGOG 3016): a randomised, controlled, open-label trial. Lancet Oncol 2013; 14: 1020–1026.
19. Dunleavy K, Pittaluga S, Maeda LS et al. Dose-adjusted EPOCH-rituximab therapy in primary mediastinal B-cell lymphoma. N Engl J Med 2013; 368: 1408–1416.
20. Dunleavy K, Pittaluga S, Shovlin M et al. Low-intensity therapy in adults with Burkitt's lymphoma. N Engl J Med 2013; 369: 1915–1925.
21. Gatzemeier U, von Pawel J, Vynnychenko I et al. First-cycle rash and survival in patients with advanced non-small-cell lung cancer receiving cetuximab in combination with first-line chemotherapy: a subgroup analysis of data from the FLEX phase 3 study. Lancet Oncol 2011; 12: 30–37.