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Total toxicity burden as a practical tool to quantify the overall severity of multiple adverse events in clinical trials

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INTRODUCTION

Phase I clinical trials (CT) are the standard of care to proof new drugs are safe [1, 2]. Adverse events (AEs) are reported using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, categorized into 5 grades [3].

An enormous amount of AEs data per patient is created per clinical trial, which is hard to quantify and report. The total toxicity burden (TTB) summarizes the overall AEs per patient during a clinical trial into a single quantifiable number [4].

We believe this is a more precise and objective way of reporting AE.

OBJECTIVES

We aimed to calculate the TTB in phase I trials from MD Anderson Cancer Center, and to compare the TTB between groups of drugs.

METHODS

Patients treated from 2016 to 2022 in the phase I CT unit at MD Anderson Cancer Center were included.

Clinical baseline prognostic factors [ECOG, age, Carlson comorbidity index (CCI)] were included and analyzed. AEs according to the CTCAE v5.0 were collected and simplified into 21 categories per trial and patient.

Treatments were divided into: Cytotoxic agents (Chemo), Targeted Therapy (TT), Immune checkpoint inhibitors (ICI), Chimeric antigen receptor T cells (CART), or Cytokines (CYT). Using regimen-related AEs for evaluable patients, mean (SD)

TTB for each treatment group was computed using each patent's worst grade as the severity weight for each type of AE.

To estimate the average treatment effects (ATE) among the four major groups (cytotoxic agents, targeted agents, immunotherapy, and cytokine agents), we used inverse probability weighting (IPTW) with propensity scores to adjust for patient baseline variables. The propensity scores were constructed using a logistic regression model based on selected patient baseline variables, including age, sex, race, ethnicity, number of prior treatment lines, ECOG score, and Charlson index. A standardized mean difference (the mean divided by the standard deviation of a difference) within the range of -0.1 to 0.1 was considered balanced. After IPTW, linear regression with the same covariates used for propensity score model was conducted for TTB, and the final ATE in terms of TTB was obtained using g-computation approach. For grade >=3 AE rates, IPTW-based logistic regression and the g-computation approach were used. The p-values were derived from the Z-test.

RESULTS

Table 1: Population Characteristics per Drug Group.

		Cytotoxic (N=129)	Targeted (N=429)	Immunotherapy (N=649)	CAR T (N=21)	Cytokine (N=94)	P-value
Age	Mean (SD)	59.3 (11.6)	57.3 (13.3)	58.7 (13.5)	59.4 (13.6)	61.1 (12.3)	0.0903
	Median [Min, Max]	61.0 [28.0, 79.0]	60.0 [19.0, 90.0]	61.0 [20.0, 92.0]	64.0 [30.0, 84.0]	64.0 [30.0, 86.0]	
ECOG	0	25 (19.4%)	119 (27.7%)	152 (23.4%)	3 (14.3%)	20 (21.3%)	0.174
	1	104 (80.6%)	310 (72.3%)	497 (76.6%)	18 (85.7%)	74 (78.7%)	
Race	White	98 (76.0%)	342 (79.7%)	504 (77.7%)	16 (76.2%)	73 (77.7%)	0.747
	African American	11 (8.5%)	37 (8.6%)	63 (9.7%)	0 (0%)	9 (9.6%)	
	Asian	10 (7.8%)	19 (4.4%)	34 (5.2%)	1 (4.8%)	5 (5.3%)	
	Others or Unknown	10 (7.8%)	31 (7.2%)	48 (7.4%)	4 (19.0%)	7 (7.4%)	
Ethinicty	Hispanic	15 (11.6%)	46 (10.7%)	69 (10.6%)	2 (9.5%)	10 (10.6%)	0.993
	Non-Hispanic	112 (86.8%)	372 (86.7%)	566 (87.2%)	19 (90.5%)	81 (86.2%)	
	Unknown	2 (1.6%)	11 (2.6%)	14 (2.2%)	0 (0%)	3 (3.2%)	
Sex	Male	57 (44.2%)	183 (42.7%)	326 (50.2%)	8 (38.1%)	49 (52.1%)	0.0906
	Female	72 (55.8%)	246 (57.3%)	323 (49.8%)	13 (61.9%)	45 (47.9%)	
Prior Lines	0	82 (63.6%)	285 (66.4%)	363 (55.9%)	11 (52.4%)	64 (68.1%)	0.00411
	1	47 (36.4%)	144 (33.6%)	286 (44.1%)	10 (47.6%)	30 (31.9%)	
Charlson	<=6	28 (21.7%)	107 (24.9%)	153 (23.6%)	6 (28.6%)	17 (18.1%)	0.483
	Index	32 (24.8%)	100 (23.3%)	135 (20.8%)	2 (9.5%)	15 (16.0%)	
	8	43 (33.3%)	132 (30.8%)	202 (31.1%)	6 (28.6%)	37 (39.4%)	
	>=9	26 (20.2%)	90 (21.0%)	159 (24.5%)	7 (33.3%)	25 (26.6%)	
≥G3 Toxicity	Yes	28 (21.7%)	90 (21.0%)	79 (12.2%)	11 (52.4%)	6 (6.4%)	<0.001
	No	101 (78.3%)	339 (79.0%)	570 (87.8%)	10 (47.6%)	88 (93.6%)	
TTB	Mean (SD)	2.66 (3.30)	2.89 (3.60)	1.73 (2.86)	5.95 (5.08)	0.819 (1.78)	<0.001
	Median [Min, Max]	2.00 [0, 18.0]	2.00 [0, 20.0]	0 [0, 25.0]	6.00 [0, 16.0]	0 [0, 9.00]	

Figure 1: Drug Group Comparisonsbased on IPTW.

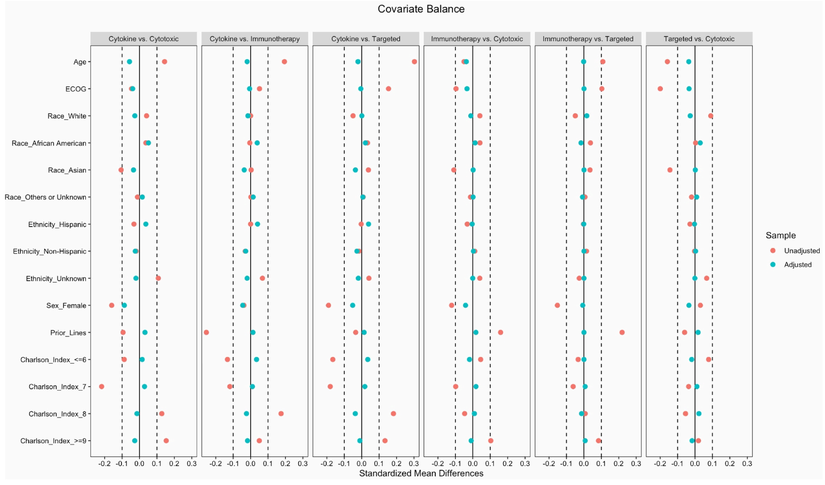


Table 2: IPTW-adjusted estimates of the TTB and grade >= 3 AE

Group	Grade >= 3 AE rate		Total toxicity burden	
	Estimate	Standard error	Estimate	Standard error
Cytotoxic	23.1%	0.038	2.65	0.30
Targeted	21.4%	0.020	2.89	0.17
Immunotherapy	11.9%	0.013	1.72	0.11
Cytokine	7.8%	0.022	0.87	0.20

Table 3: IPTW-adjusted average treatment effects between study drugs

Comparison	Grade >= 3 AE rate		Total toxicity burden	
	ATE	p-value	ATE	p-value
Immunotherapy - Cytotoxic	-11.2%	0.006	-0.93	0.004
Immunotherapy – Targeted	-9.5%	<0.001	-1.17	<0.001
Immunotherapy - Cytokine	4.1%	0.111	0.85	<0.001
Cytotoxic – Targeted	1.7%	0.702	-0.24	0.481
Cytotoxic – Cytokine	15.2%	<0.001	1.78	<0.001
Targeted - Cytokine	13.6%	<0.001	2.02	<0.001

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CONCLUSIONS

- Total toxicity burden (TTB) is a useful tool to quantify the mean severity of qualitatively different types of adverse events experienced by patients in a clinical trial, and mean TTB is useful to easily compare toxicities between treatment groups.
- Severe toxicity events (≥G3) capture the drug toxicity, but TTB comparisons offer greater precision by providing a more comprehensive analysis of each patient's toxicity profile.

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