

RESEARCH LETTER

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Chemotherapy-induced anaphylaxis and fatal anaphylaxis in the United States: Incidence and risk factors

Drug-induced anaphylaxis (DIA) is the most common cause of fatal anaphylaxis in the United States and other countries.¹ After antibiotics and contrast agents, chemotherapeutic medications are the third leading cause of fatal DIA in the United States.¹ However, the incidence of anaphylaxis to chemotherapeutic medications is unknown.² In this study, we sought to analyse the incidence and risk factors of anaphylaxis secondary to chemotherapy agents in the United States.

Following the methodology that we used in a previous report,³ we used the Nationwide Inpatient Sample from 2004 to 2014. We identified cases of patients receiving chemotherapy using clinical classification code 224 (cancer chemotherapy). We also used the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9CM) code to identify cases of anaphylaxis with the code 995.0 (other anaphylactic reaction), as well as the combination of any of the following codes: 995.3 (allergy, unspecified) or 995.2 (adverse drug effect), or E930-E949 (drugs, medicinal and biological substance causing adverse effects in therapeutic use) plus 458.9 (hypotension) and either 519.11 (bronchospasm) or 786.1 (stridor).³ Relationships between groups for categorical variables were evaluated using chi-square tests. Continuous variables were evaluated using Kruskal-Wallis tests. Data were not available for analysis of the following variables: paralysis, chronic blood loss anaemia, rheumatoid arthritis/collagen vascular disease and acquired immunodeficiency syndrome. For the multivariable analysis, we removed variables marked as not included (NI) which were not statistically significant on univariate analysis (Table 2) for logistic and cox regression (with Bonferroni correction). Analysis was completed using SAS version 9.4 (Cary, N.C.). Informed consent was waived since we used deidentified, available data from a national data set.

A total of 336,610 patients received chemotherapeutic medications between 2005 and 2014. As many as 209 (0.06%) patients developed anaphylaxis and four died (1.9%). In the chemotherapy-induced anaphylaxis group, the mean age was 40 (± 9.13); 52.6% were female, and 69.4% were white. Patients with anaphylaxis had higher total hospital costs (median \$38,226) compared with hospitalized patients receiving chemotherapy without anaphylaxis (median \$25,344) ($p < .0001$). The length of stay, race or US region was not significantly affected in patients with anaphylaxis compared with controls (Table 1). Risk factors for chemotherapy-induced anaphylaxis included age group younger than 18 years old (OR, 2.9; 95% CI, 1.3–6.3; $p < .0001$), female sex (OR, 1.7; 95% CI, 1.2–2.5;

Key Messages

- The incidence of chemotherapy-induced anaphylaxis in the United States is 1 in 1,611.
- Risk factors for chemotherapy-induced anaphylaxis include female sex, age and some comorbid conditions.
- Serum tryptase and allergist referral should be obtained in patients with suspected drug-induced anaphylaxis.

$p = .004$) and comorbid conditions of metastatic disease (OR, 3.8; 95% CI, 2.1–6.5; $p < .0001$), lymphoma (OR, 8.1; 95% CI, 4.1–16.1; $p < .0001$), solid tumour (OR, 2.9; 95% CI, 1.2–6.6; $p = .01$) and hypothyroidism (OR, 2.2; 95% CI, 1.2–3.9; $p = .01$) (Table 2). Chronic lung disease which includes asthma in NIS revealed an increased risk for chemotherapy-induced anaphylaxis on univariate analysis but was lost in multivariable analysis (Table 2).

We report an estimated 209 chemotherapy-induced anaphylaxis cases between 2005 and 2014. The rate of anaphylaxis caused by chemotherapy medications was 0.06% with a 1.9% mortality rate. A similar mortality rate has been reported by Jerschow et al; where out of a total of 2458 cases of fatal anaphylaxis in the United States, there were 46 (1.8%) cases of fatal anaphylaxis due to chemotherapy medications.¹ Patients with chemotherapy-induced anaphylaxis also had higher costs of hospitalization compared with controls. Female sex, age <18 years old and the presence of lymphoma, solid tumours or metastatic disease were associated with a higher risk of developing chemotherapy-induced anaphylaxis. Our study supports previous literature reporting a higher frequency of drug allergy and DIA in women. It has been described that this propensity develops after puberty, likely related to immunomodulatory effects of oestrogen.^{4–6} Our findings differ from previous reports suggesting higher rates of DIA in adults compared with children.^{4,6} However, it is important to clarify that the drugs most associated with anaphylaxis in adults were antibiotics. Conversely, non-antibiotic medications were most frequently associated with anaphylaxis in children, which could be the reason as to why in our study children had higher odds of anaphylaxis compared with adults. A previous study showed that hypothyroidism was associated with decreased odds for DIA (OR 0.85).⁷ On the contrary, our study found that hypothyroidism was a risk

TABLE 1 Characteristics of chemotherapy-induced anaphylaxis, 2005–2014

Characteristic	Chemotherapy without anaphylaxis cases (n = 336,610) (%)	Chemotherapy-induced anaphylaxis cases (n = 209) (%)	p value
Age			
Median (IQR)	51 (23,64)	47 (14,62)	.006
Mean (SD)	45 (23.66)	40 (25)	
Groups			
<18	68399 (20)	67 (32)	.0003
18–34	39396 (12)	17 (8)	
35–64	150677 (45)	83 (40)	
≥65	78138 (23)	42 (20)	
Sex			
Male	184934 (55)	99 (47)	.03
Female	151676 (45)	110 (53)	
Race			
White	186938 (65)	127 (70)	<.0001
Black	36660 (13)	12 (7)	
Hispanic	41958 (15)	29 (16)	
Asian or Pacific Islander	11398 (4)	7 (4)	
Native American	1408 (0.5)	1 (0.5)	
Other	9930 (3)	6 (3)	
Unknown	68705 (20)	26	
Region			
Northeast	70737 (21)	28 (13)	.007
Midwest	65102 (19)	53 (25)	
South	132066 (39)	76 (36)	
West	68705 (20)	52 (25)	
Teaching hospital status			
Non-teaching	54295 (22)	32 (27)	.26
Teaching	187743 (78)	88 (73)	
Missing	94572	89	
Admission type			
Non-elective	2 (0)	0 (0)	.03
Elective	134688 (40)	102 (49)	
Missing	200792 (60)	105 (51)	
Length of stay			
Mean (SD)	5.7 (7.4)	7.0 (9)	.71
Median (Range)	4 (0–243)	4 (0–54)	
Total charges			
Mean (SD)	44367.2(69846.80)	70984.7(121473.48)	<.0001
Median (Range)	25344(35, 3358809)	38226(1284,1359363)	
Mortality	4039 (1.2)	4(1.9)	.34

Abbreviations: IQR, Interquartile interval; SD, Standard deviation.

factor for the development of anaphylaxis on univariate and multivariate analyses. We uncovered an important trend of increased odds of anaphylaxis in patients with lymphoma, solid tumours and metastatic disease, which are not well described in the literature thus far. A possible explanation is that the release of cytokines is

directly related to the bulk of the disease and that increased tumour burden leads to increased release of cytokines on various immune cells, leading to their activation and lysis once exposed to chemotherapeutic agents. It is also possible that increasing odds of anaphylaxis in patients with metastatic disease could be related to prior

TABLE 2 Predictors of chemotherapy-induced anaphylaxis (n = 209)

Characteristic	Univariate		Multivariable	
	OR (95% CI)	p value	OR (95% CI)	p value
Age				
<18	1.65 (1.30–2.08)	<.001	2.9 (1.3–6.3)	<.0001
18–34	Reference		Reference	
35–64	0.93 (0.74–1.16)	.49	1.2 (0.5–2.7)	.60
≥65	0.9 (0.69–1.18)	.46	0.9 (0.4–2.2)	.08
Sex				
Female	1.36 (1.03–1.78)	.03	1.7 (1.2–2.5)	.004
Male	Reference		Reference	
Race				
White	Reference		1.3 (0.9–1.9)	.16
Non-White	1.24 (0.94–1.64)	.13	Reference	
Teaching hospital status				
Teaching	0.8 (0.53–1.19)	.26	0.7 (0.5–1.1)	.15
Non-teaching	Reference		Reference	
Admission type				
Elective	0.69	.008	0.9 (0.6–1.2)	.53
Non-elective	Reference		Reference	
Comorbidity measures				
Metastatic cancer	3.8 (2.62–5.51)	<.001	3.8 (2.1–6.5)	<.0001
Lymphoma	5.34 (3.10–9.19)	<.001	8.1 (4.1–16)	<.0001
Solid tumour without metastasis	2.64 (1.40–4.98)	.003	2.9 (1.2–6.6)	.01
Hypothyroidism	1.93 (1.23–3.03)	.004	2.2 (1.2–3.9)	.01
Coagulopathy	1.74 (1.15–2.65)	.009	1.2 (0.6–2.3)	.56
Alcohol abuse	2.53 (1.12–5.71)	.03	2.1 (0.5–8.7)	.30
Fluid & electrolyte disorders	1.45 (1.03–2.02)	.03	1.1 (0.7–1.9)	.57
Chronic pulmonary disease	1.53 (1.02–2.31)	.04	0.9 (0.5–1.8)	.83
Neurological disorder	1.76 (0.98–3.15)	.05	NI	
Pulmonary circulation disorders	2.09 (0.78–5.62)	.14	NI	
Weight loss	1.51 (0.84–2.71)	.16	NI	
Renal failure	0.62 (0.23–1.67)	.34	NI	
Obesity	1.42 (0.73–2.78)	.30	NI	
Liver and biliary disease	0.6 (0.19–1.89)	.38	NI	
Deficiency anaemia	1.13 (0.80–1.59)	.49	NI	
Diabetes mellitus with complications	0.47 (0.07–3.36)	.61	NI	
Diabetes mellitus, uncomplicated	1.12 (0.73–1.71)	.45	NI	
Hypertension	0.92 (0.68–1.26)	.61	NI	
Depression	0.91 (0.53–1.57)	.74	NI	
Congestive heart failure	0.87 (0.32–2.33)	.77	NI	
Drug abuse	0.87 (0.22–3.49)	.84	NI	
Peripheral vascular disorder	0.86 (0.21–3.47)	.83	NI	
Psychoses	1.09 (0.41–2.94)	.85	NI	
Valvular disease	1.05 (0.34–3.28)	.93	NI	

Abbreviations: CI, Confidence interval; NI, Not included.

exposure to multiple chemotherapeutic agents, developing sensitization and increased risk of anaphylactic reactions with subsequent doses. Moreover, by analysing the cases of hypersensitivity reactions and anaphylaxis associated with frequently used medications used in the treatment of these conditions, we may gain some insight as to the possible link between the increased odds for anaphylaxis in patients with lymphoma, solid tumours and metastatic disease.^{1,8,9}

Some limitations of this study warrant further discussion. We were unable to determine the culprit chemotherapeutic agent(s) for the anaphylactic reactions since the NIS is composed of administrative, deidentified data from multiple hospitals across the United States, with pre-specified variables. And although reviewing each chart would be useful for determination of culprit agents, number of exposures to the agent (especially for taxanes and platinated agents), tryptase levels and referral to an allergy department, the data used were deidentified and chart review was unavailable. Additionally, it is possible that the most prominent symptom of the anaphylactic reaction was coded as opposed to anaphylaxis itself. The use of large databases such as the NIS is inherently limited by the different coding methods across different institutions. Nevertheless, the use of such large datasets likely makes results generalizable to similar populations in the United States. Further prospective studies are warranted to evaluate the differences in the rates of anaphylaxis between different chemotherapeutic agents and the number of exposures to them.

Events of chemotherapy-induced anaphylaxis usually do not occur during the first exposure to the drug, and this is especially well studied in platinum agents. Taxanes, however, usually cause anaphylaxis during the first or second exposure.¹⁰ When encountered with a patient with possible anaphylaxis to any chemotherapeutic agent, measurement of an acute and baseline serum tryptase level and a referral to an allergy healthcare provider for further evaluation of the index reaction are of utmost importance to phenotype these reactions and perform a chemotherapy desensitization if indicated.

KEYWORDS

allergens and epitopes, anaphylaxis, clinical immunology, drug allergy, epidemiology

CONFLICTS OF INTEREST

The authors declare that they have no relevant conflict of interest.

AUTHOR CONTRIBUTION

Author personal contributions were as follows: Leyla Bojanini, M.D.: conceptualized and designed; involved in acquisition of data, analysed and interpreted the data; drafted the article; and reviewed it critically for important intellectual content. Dan Morgenstern-Kaplan, M.D.: conceptualized and designed; analysed and interpreted the data; drafted the article; and reviewed it critically for important intellectual content. Ismael Carrillo-Martin, M.D.: conceptualized and designed; analysed and interpreted the

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ETHICS STATEMENT

IRB/Ethics committee approval was waived since the data used are deidentified and available in a national database. No informed consent was needed.

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None.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from The National Inpatient Sample. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the author(s) with the permission of The National Inpatient Sample.

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