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Preoperative leukopenia does not affect outcomes in cancer patients undergoing elective and emergent abdominal surgery: A brief report

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ABSTRACT

Background: Leukopenic patients have historically been considered poor surgical candidates due to a perceived increase in operative morbidity and mortality.
Methods: Retrospective cohort study using the NSQIP database to identify adult patients who received chemotherapy for malignancy within 30-days prior to elective or emergent abdominal surgery between 2008 and 2011. Leukopenia was defined as < 4000 WBC/mm^3 within 2-days prior to surgery. Multiple logistic regression assessed if leukopenia was associated with morbidity and mortality.
Results: Of the 4369 patients included, 20.2% had preoperative leukopenia. Emergency cases comprised 36.2% of cases. Overall 30-day mortality was 12.2% and 30-day composite morbidity was 29.8%. After controlling for significant confounders, including emergency status, leukopenia was not significantly associated with either postoperative mortality ($p = 0.14$) or morbidity ($p = 0.17$).
Conclusions: Our study suggests that in cancer patients undergoing chemotherapy, leukopenia is not associated with morbidity or mortality and should not influence operative planning in either the elective or emergent setting.

Background

Patients receiving cytotoxic chemotherapy for malignancy frequently develop leukopenia, placing them at increased risk for potentially life-threatening infections. This chemotherapy-associated leukopenia can be exacerbated by decreased bone marrow reserves and an impaired ability to mobilize leukocytes. The degree and duration of leukopenia vary by tumor type, therapeutic modality, and patient factors. Although most common with hematologic malignancies, all patients with leukopenia after chemotherapy have historically been considered poor surgical candidates due to a perceived increase in operative morbidity and mortality.[1,2] As such, surgeons tend to recommend nonoperative or delayed operative management pending bone marrow recovery.[2,3] More recent studies have questioned this perception, showing no correlation between leukopenia and surgical outcomes; however, most of these studies were conducted only in the elective setting.[4,5] With the goal of understanding if surgery should be delayed pending bone marrow recovery, we compared morbidity and mortality in a large cohort of patients undergoing elective and emergent abdominal surgery to determine if leukopenia was associated with worse outcomes.

Methods

Study design and setting

We performed a retrospective cohort study using the American College of Surgeons (ACS) National Surgical Quality Improvement Program (NSQIP) database between 2008 and 2011. The NSQIP database contains over 250 prospectively collected data points for patients from over 250 hospitals, including preoperative risk factors, laboratory values, intraoperative variables, and 30-day postoperative morbidity and mortality outcomes. All information is de-

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identified and a Data Use Agreement was signed prior to gaining database access. All patients ≥18-years-old who received chemotherapy for malignancy within 30-days of abdominal surgery were included. In the NSQIP database, chemotherapy "may include, but is not restricted to, oral and parenteral treatment with chemotherapeutic agents for malignancies such as colon, breast, lung, head and neck, and gastrointestinal solid tumors as well as lymphatic and hematopoietic malignancies such as lymphomas, leukemias, and multiple myeloma".[6] Abdominal surgery was defined by the Current Procedural Terminology (CPT) codes for surgery of the gastrointestinal and hepatobiliary systems, adrenal glands, and spleen, as well as hernia surgery. Surgery was categorized by elective or emergent status. Emergency surgery was defined as surgery "performed as soon as possible and no later than 12-h after the onset of related preoperative symptomatology".[6] Data collected included patient demographics, comorbidities, preoperative laboratory values, and operative details.

Exposure variable

Concordant with the NSQIP definition and other papers on this topic, we defined leukopenia as < 4000 WBC/mm^3 within 2-days prior to surgery.[6,7]

Outcomes

Primary outcomes were 30-day postoperative morbidity (surgical site infection, all infections, unplanned return to the operative room, blood transfusion requirement, coma >24-h, wound disruption, and combined cardiovascular, pulmonary, and septic complications), and mortality.

Statistical analysis

To identify potential confounding factors for leukopenia in 30-day morbidity and mortality, the association of leukopenia to various demographic, clinical, and operative characteristics was evaluated using chi-square tests for discrete variables and Student's t-tests for continuous variables. The association of each of these factors with morbidity and mortality was also tested with univariate statistics. Factors that were significantly associated with leukopenia and morbidity or mortality were included in a multiple logistic regression model.[8] Univariate statistics and multiple logistic regression were also used to determine if preoperative WBC was associated with morbidity and mortality. In a sensitivity analysis we used WBC as a continuous variable. STATA software was used for all analyses.[9]

Results

4384 patients met inclusion criteria for our study. Of these, 2779 (63.4%) patients underwent elective surgery and 1605 (46.6%) were emergency cases. Overall, 891 (20.3%) patients were leukopenic. Compared with non-leukopenic patients, leukopenic patients were significantly less likely to be functionally independent preoperatively and more likely to have high American Society of Anesthesiologists (ASA) and wound classes ($p < 0.001$) (Table 1). Thirty-day composite morbidity and 30-day mortality rates were 29.8% (1306 patients) and 12.1% (534 patients), respectively. Morbidity and mortality were 34.0% and 15.3% in leukopenic compared to 28.7% and 11.4% in non-leukopenic patients ($p = 0.002$, $p = 0.002$). After controlling for significant confounding factors, including emergency status, tobacco use, functional status, ASA class, wound class, age, and preoperative blood urea nitrogen (BUN), leukopenia was not associated with either morbidity (Table 2) ($p = 0.17$) or mortality (Table 3) ($p = 0.14$). Tables 2 and 3 report the odds ratios for leukopenic patients compared to non-leukopenic patients; there was no difference in the odds of morbidity or mortality for leukopenic and non-leukopenic patients. Additionally, there was no interaction of emergency status and leukopenia for either morbidity or mortality, meaning that emergency status did not alter the association of leukopenia with either outcome. When analyzed as a continuous variable, preoperative WBC was significantly related to morbidity on univariate analysis ($p = 0.006$), but not in the multiple logistic regression model.

Table 1
Patient characteristics.

	Non-Leukopenic n = 3493 (79.7%)		**Leukopenic n = 891 (20.3%)**		*P*-value
Preoperative Characteristics					
Male gender	1745	(50.2%)	452	(50.7%)	p = 0.69
DNR status	111	(3.2%)	30	(3.4%)	p = 0.78
Independent functional status	3038	(87.0%)	735	(82.5%)	p < 0.01
Chronic steroid use	398	(11.4%)	124	(13.9%)	p = 0.33
Radiotherapy within 6-months	636	(18.2%)	175	(19.6%)	p = 0.33
Current tobacco use	636	(18.2%)	171	(19.2%)	p = 0.96
ASA Classification[a]					p < 0.01
Class I	26	(7.4%)	3	(0.3%)	
Class II	534	(15.3%)	124	(13.9%)	
Class III	2180	(62.4%)	502	(56.3%)	
Class IV	707	(20.2%)	230	(25.8%)	
Class V	46	(1.3%)	32	(3.6%)	
Wound Classification					p < 0.01
Class I – clean	406	(11.6%)	108	(12.1%)	
Class II – clean/contaminated	1826	(52.3%)	418	(46.9%)	
Class III – contaminated	434	(12.4%)	143	(16.0%)	
Class IV – dirty/infected	827	(23.7%)	222	(24.9%)	

[a] American Society of Anesthesiologists (ASA) Classification.

Discussion

This study reports on a large group of leukopenic patients undergoing elective and emergent abdominal surgery. Our results demonstrated no significant increase in 30-day postoperative morbidity and mortality in leukopenic patients undergoing surgery within 30-days of chemotherapy for malignancy, even when stratified by elective and emergent status. This suggests that the presence of leukopenia alone should not bar a patient from the operating room. Other studies have shown similar outcomes in patients undergoing scheduled oncologic resections after chemotherapy.[4,5] For emergency surgery, however, studies have shown worse outcomes in leukopenic patients.[7] The lack of association between emergency surgery, leukopenia, and postoperative morbidity and mortality in our analysis could be explained by several phenomena. First, our cohort of leukopenic patients may have experienced better outcomes than historical comparisons due to advances in medical care, including more effective antibiotics,

Table 2
Multiple logistic regression on 30-day morbidity.

	Odds Ratio	95% Confidence Interval
Leukopenia	1.13	0.95–1.34
Emergency Surgery	1.15	0.98–1.35
Functional Status	1.29	1.15–1.46
ASA Class	1.30	1.16–1.47
Wound Class	1.21	1.12–1.30
Steroid Use	1.21	0.98–1.48

Table 3
Multiple logistic regression on 30-day mortality.

	Odds Ratio	95% Confidence Interval
Leukopenia	1.20	0.94–1.53
Emergency Surgery	1.46	1.14–1.84
Tobacco Use	1.30	1.01–1.68
Functional Status	1.61	1.41–1.85
ASA Class	2.20	1.85–2.61
Wound Class	1.11	1.00–1.24
Age	1.01	1.00–1.02

the widespread use of colony stimulating factors, improvements in critical care, and enhanced recovery protocols. Second, the NSQIP database is a sample of patients undergoing operative management only, so surgeons may have selected for patients with a better prognosis. For instance, they may have primarily chosen to operate on leukopenic patients with an up-trending WBC, which we were unable to determine using the database.

Although performed on a larger sample than some of the more recent literature, our study did have several limitations. As a retrospective database study, we were limited to data points collected by NSQIP, so we were unable to stratify our sample by the type of cancer, the duration of leukopenia, the trend in WBC, or the duration of chemotherapy. These factors likely influenced the degree of immunosuppression at the time of surgery and may have played an important role in determining postoperative outcomes. In the elective cohort, the inability to account for these factors could have led to a biased selection of patients with better preoperative optimization. Another major limitation to our study was the use of leukopenia as a proxy for neutropenia, which is not a datapoint captured by the NSQIP dataset. Although leukopenia typically results from absolute neutropenia, there are exceptions.[10] Despite these limitations, our results do question conventional surgical training regarding the management of leukopenic patients; they suggest that the presence of leukopenia alone should not dissuade surgeons from pursing aggressive, life-saving measures in leukopenic patients. Further studies should be done to confirm our results, particularly for patients undergoing emergency surgery.

Declaration of competing interest

Heather M. Grant: no conflicts of interest to declare.
Lindy L. Davis: no conflicts of interest to declare.
Jane Garb: no conflicts of interest to declare.
Richard B. Arenas: no conflicts of interest to declare.
Jay N. Kuhn: no conflicts of interest to declare.
Mihaela S. Stefan: no conflicts of interest to declare.

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