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RESEARCH ARTICLE

Bacteremia in Cancer Patients as a Prognostic Factor and the Relationship with Chemotherapy

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ABSTRACT

Introduction: Bacteremia is a cause of morbi-mortality in cancer patients, due to its severity, longer hospital stays, chemotherapy withdraw, and increased costs. The study aimed to clarify if bacteriemia in cancer patients is associated with higher mortality rates and alert the community to this emerging problem.

Methods: The authors collected every cancer patient hospitalized in our cancer center, who developed bacteremia during their stay in hospital or at admission, in the last 9 years. Data was treated with SPSS. The p-values <0.05 were considered to be statistically significant.

Results: From 204 bloodstream infections, almost half of the patients had gastrointestinal cancer (49%). Males were predominant (54,4%) and the median age was 66 years-old. The catheter-totally-implanted was responsible in 38,7% of the cases. From all bacteria, 20,5% were multidrug-resistant and 48% were resistant to at least one antibiotic. From all patients, 61,5% received chemotherapy the month before the infection. The survival of those that did received chemotherapy was significantly different from patients that did not, $t(203)= 2,06$, $p=0,04$. Chemotherapy the month before was correlated with lower survival rates, $r(203)=-0,15$, $p=0,03$, and Kaplan-Meyer curve showed a tendency towards statistical significance ($p=0,06$). The stage of the oncologic disease was not associated with the mortality of the patient ($p>0,05$). The infection contributed or was the cause of death in 45% of the patients. The 3 months mortality rate of the patients that had bacteriemia was 74,5%.

Conclusion: Currently there are no guidelines regarding prescription of antimicrobial therapy in cancer patients. Three quarters of the cancer patients that suffer bacteriemia died in 3 months, and active chemotherapy treatment is associated with lower survival rates.

Keywords: oncology; bloodstream infection; multidrug-resistant bacteria; antibiotic stewardship.

Introduction:

Bacteremia or bloodstream infection is defined as the presence of a pathological microorganism such as a fungi or a bacteria in the bloodstream, which must be confirmed with a positive blood culture.¹ If the patient develops a systemic inflammatory response due to the invasion of normally sterile tissues, we are facing a sepsis.² If this scenario figures as a major health problem to all community, it constitutes an even higher problem to cancer patients, who are affected by pathological or pharmacological conditions that are predisposed to infections. The ability of a microorganism to cause disease is dependent of its virulence, immunological competence of the host, and disruption of its defense barriers.³

Bacteremia is a cause of morbi-mortality in cancer patients, due to its severity, longer hospital stays, chemotherapy withdraw, and increased costs.⁴ Its prevalence ranges between 11%-38% and the mortality rate is around 40%.⁵ These numbers tend to increase with the emergence of multidrug-resistant bacteria (MDR).

The microorganisms isolated from blood cultures of cancer patients have changed during the years. When only chemotherapy was administrated, gram-negative infections were predominant.⁶ Since the generalization of indwelling catheters, gram-positive infections taken place as most infections.⁷ The

prophylactic use of antibiotics is decreasing in the majority of the institutions that treat cancer patients, leading to an increase of gram-negative infections.⁵

Nevertheless, mortality due sepsis decreased in these patients⁸, mainly because health professionals are more trained and aware of these problem, better infection control measures, better intensive care units and better treatments.

There are guidelines and accepted procedures^{9,10} for the early recognition and fast administration of antibiotic and fluid resuscitation. However, all these studies were performed and are directed to general population. High risk population such oncologic patients are excluded from these kind of recommendations.

The study aimed to clarify if bacteriemia in cancer patients is associated with higher mortality rates and alert the community to this emerging problem. Therefore, the rationale behind this study is to evaluate sepsis outcomes in the oncological population.

Methods:

The authors conducted a single-center, observational retrospective study, that included every cancer patient hospitalized in our cancer center, who developed bacteremia during their stay in hospital or at admission, in the last 9 years (between January 2010 and December 2019). Inclusion criteria included all

patients with microorganism isolation in blood culture; exclusion criteria included patients with incomplete information or isolations considered contamination. For each patient, the medical records and the microbiological analysis were reviewed. Data was treated with SPSS statistics (t-student test, pearson correlation coefficient, bivariate analysis and Kaplan-Meier Curve). The p values <0.05 were considered to be statistically significant.

Results:

A total of 204 bloodstream infections were reported, with positive cultural isolations. Males were predominant (54,4%) and the median age was 66 years old (range 28 to 89). Almost half of the patients had gastrointestinal cancer (49%), followed by breast cancer (15,7%) (Table 1).

Table 1 – Disease of patients with positive blood cultures.

Cancer type	Total – N (%)
Gastrointestinal	100 (49%)
Breast	32 (15,7%)
Head and Neck	19 (9,3%)
Urological	10 (5%)
Gynecological	10 (5%)
Central nervous system	8 (4%)
Lung cancer	8 (4%)
Sarcomas	6 (3%)
Carcinoma of unknown primary	5 (2,5%)
Melanoma	3 (1,5%)
Hematologic malignancies	3 (1,5%)

The catheter totally implanted (CTI) was responsible in 39% of the cases, 29% had no

identified focus (Table 2).

Table 2 – Source of infection in patients with positive blood cultures.

Source of infection	Total – N (%)
Catheter totally implanted	79 (39%)
No identified focus	59 (29%)
Urinary tract infections	27 (13%)
Respiratory infections	17 (8%)
Intra-abdominal infections	11 (5,5%)
Soft tissues infections	5 (2,5%)
Surgical wound infections	4 (2%)
Gastrointestinal infections	2 (1%)

The responsible microorganism was the staphylococcus aureus in 14,5% of the Escherichia coli in 25%, followed by the infections (Table 3).

Table 3 – Microorganisms isolated in blood cultures

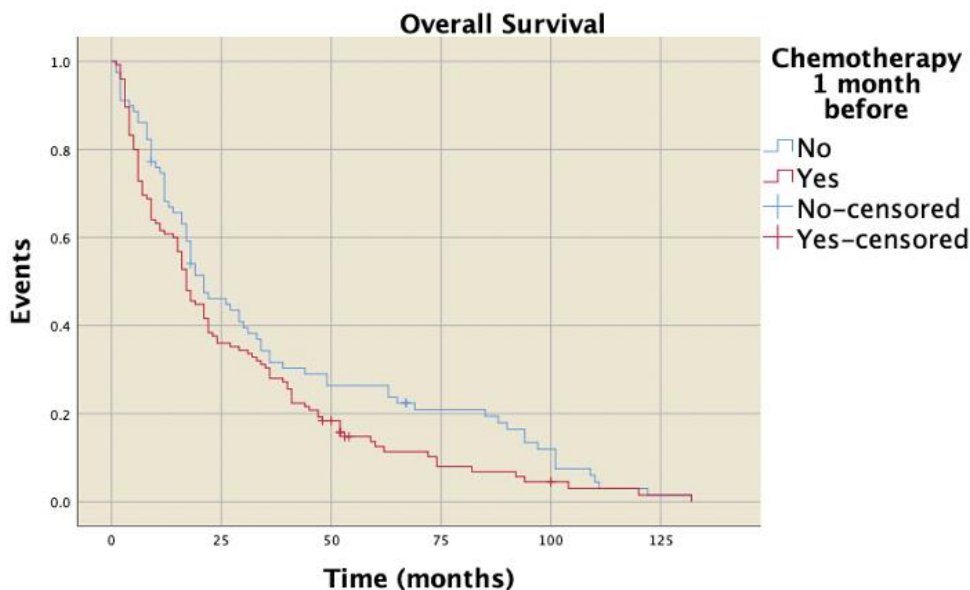
Microorganism	Total – N (%)
Escherichia coli	50 (24,5%)
Staphylococcus aureus	30 (14,7%)
Klebsiella pneumoniae	26 (12,7%)
Staphylococcus epidermidis	22 (10,8%)
Pseudomonas aeruginosa	14 (6,9%)
Coagulase negative staphylococci	13 (6,3%)
Enterococcus cloacae	13 (6,3%)
Other klebsiella	7 (3,4%)
Enterococcus faecalis	6 (2,9%)
Serratia marcescens	5 (2,5%)
Candida albicans	4 (2,0%)
Other Enterobacter	3 (1,5%)
Enterobacter faecium	2 (1,0%)
Other serratia	2 (1,0%)
Proteus mirabilis	2 (1,0%)
Streptococcus viridans	2 (1,0%)
Acinetobacter baumannii	2 (1,0%)
Other fungi	1 (0,5%)

From all bacteria, 26% were multi-drug resistant and 48% were resistant to at least one antibiotic. The staphylococcus aureus was meticilin-resistant in 37%, and 4% were carbapenemase producing organisms.

From all patients included in the study, 61,5% received chemotherapy the month before the infection. The survival of the patients that received chemotherapy was significantly different from patients that did not, $t(203)=2,06$, $p=0,04$. Chemotherapy the

month before was correlated with lower survival rates, $r(203)=-0,15$, $p=0,03$, and Kaplan Meyer curve showed a tendency towards statistically significance ($p=0,06$) (Figure 1). The stage of the oncologic disease was not associated with the mortality of the patient ($p>0,05$). The infection contributed or was the cause of death in 45% of the patients. The 3 months mortality rate of the patients that had bacteriemia was 74,5%.

Figure 1 – Kaplan Meier curve for patients that received chemotherapy before infection versus patients that did not received treatment ($p=0,06$).



Discussion:

Hospitalization due to infection is a common complication for cancer patients. Its predisposition for infection can result from the state of immunosuppression, from cancer therapy or due to the malignancy itself,

impairment of normal leukocyte function, or use of corticosteroids.^{11,12} Nowadays, sepsis is responsible for 9-10% of all cancer-related deaths.^{13,14} Despite this great problem, there is little data regarding bacteremia and sepsis in cancer patients. (Table 4)

Table 4 – Recent studies about infection and cancer patients

Author, year of publication	Population and findings
Lee JH, 2020 ¹⁵	484 patients, 539 catheters analyzed. 5,2% with central catheter associated bloodstream infection.
Sasaki T, 2020 ¹⁶	99 patients. 60,6% with gram negative peripheral venous catheter associated bloodstream infection.
Carena AA, 2020 ¹⁷	394 gram negative rods bacteremia. 42,6% being MDR.
Ota A, 2020 ¹⁸	39 cancer patients receiving chemotherapy. Bacteremia was detected in 10 patients (25,6%) at baseline and 11 (28,2%) during chemotherapy.
Jiang M, 2020 ¹⁹	26 studies, 5575 patients with central line associated bloodstream infection. Totally implantable venous access ports were associated with a significantly lower risk of central line associated bloodstream infection than external central venous catheters.
Stoclin A, 2020 ²⁰	77 catheter-related bloodstream infection in intensive care unit. Bloodstream infection was not associated with higher risk of intensive care unit mortality.
Garrido MM, 2019 ²¹	210 patients with bloodstream infection. Comparison between solid and hematologic malignancies.
Trecarichi EM, 2019 ²²	342 bloodstream infections caused by E. Coli in haemato-oncologic patients. 25,7% were resistant to third generation cephalosporins.
Dandoy CE, 2019 ²³	957 bloodstream infections in pediatric haemato-oncologic patients. 37% were associated with at least 1 adverse outcome.
Lubwana M, 2019 ²⁴	170 patients with febrile neutropenia. 14,1% have positive blood cultures. 85% of the isolated Enterobacteriaceae were resistant to 3 or more antibiotics. 41% were extended spectrum beta-lactamases.
Vinker-Shuster M, 2019 ²⁵	270 children with cancer. 24% developed gram-negative rod bacteremia and 10% were carbapenem resistant.

Author, year of publication	Population and findings
Widmer AF, 2019 ²⁶	15988 patients receiving high-dose chemotherapy for hematologic malignancy. Incidence rate of bloodstream infection was 14,7, 8,7 and 4,7 per 1000 patient-day in 1 st , 2 nd and 3 rd week of neutropenia.
Vahedian-Ardakani HA, 2019 ²⁷	212 patients with febrile neutropenia. 84,9% gram negative bacteremia.
Knight T, 2019 ²⁸	113 positive blood cultures. 50% of pseudomonas aeruginosa were resistant to meropenem. Pseudomonal isolates were significantly less sensitive to meropenem in the pediatric oncology group vs in the general pediatric group (50% vs 89%, p=0,003).
Allaway Z, 2019 ²⁹	15 studies, 4106 episodes of nonneutropenic fever in children with cancer. The pooled average bacteremia rate was 8,2%.
Mohan M, 2019 ³⁰	282 patients, 363 autologous stem cell transplantation. 13% bacteremia. Most frequent species were enterococcus faecium (23%) and 93% were vancomycin resistant. Bacteremia was associated with significantly decreased survival.

The majority of bacteremia studies have looked at general population and did not include oncological patients. Angus et al showed that cancer patients with a severe infection have a 30% higher risk of death compared with non-cancer patients.³¹ Williams M and colleagues concluded that mortality for cancer patients with sepsis was 52% higher than noncancer patients, the risk of severe sepsis was 1,8 times higher for solid tumor than general population, and it is independent of age.¹³ In our study, infection contributed or was the cause of death in 45% of the patients. The 3 months mortality rate of the patients that had bacteriemia was 74,5%.

Bacteremia incidence and mortality varies widely among tumor types. There are studies that had the higher infection rate in cancer of the lung and bronchus¹³, and other gastrointestinal cancers³². In our study the main diagnosis was gastrointestinal cancer, justified by the authors with the higher rate of patients treated in our center with gastrointestinal and breast cancer. On the other hand, the outcome of death was independent of the stage of the disease, meaning that the prognosis is poor even in a non-metastatic disease.

Regarding the site of infection, Dagher et al compared cancer patients with non-cancer

patients. In cancer cohort it was the respiratory system the most common site of infection, in non-cancer patients it was urinary tract infections.^{32,33} In our study the main cause of bacteremia was the catheter totally implanted, and one possible explanation is the fact all patients with gastrointestinal cancer possess this kind of catheter. However, the incidence of catheter related infections varies greatly among studies, from 5% to 60%.^{15,16,34} *Escherichia Coli* was the microorganism more often isolated in blood cultures, in accordance with the literature.^{32,33,35} Knowledge of local epidemiology and resistance patterns is crucial for antimicrobial agents' choice.

One possible confounding factor in oncological patients is the stage of the disease, having a stage IV disease yields higher mortality than minor stages. However, the bivariate analyses showed no association between the staging and the mortality of the patients in our sample.

For a long time, cancer patients were not admitted to intensive care units due to their poor prognosis. The survival of oncologic patients who are accepted to the intensive care units due to severe sepsis has notably improved over the last decades and now exceeds 50%.³¹ Routinely, admissions without limits of resources are applied to patients treated with curative intent, those in remission of their malignancy and patients that,

although cure is not possible, had a long-expected life.³⁷ Treatment goals and prognosis must be discussed with the families and patient before admission in intensive care unit, re-evaluated daily and communicated to the family.³⁸

Dealing with sepsis in a cancer patient is challenging, since in both cases the immune system is dysregulated. In the case of sepsis, innate and adaptative systems are inoperative due to excessive release of inflammatory cytokines.³⁹ In case of cancer, patients have decreased antigen presentation and quantitative and functional defects in lymphocytes which limits the response to an external aggression.⁴⁰ All this effect is more notorious when cytostatic treatment is given.

To our knowledge, this is the first published study where the incidence of bacteremia was related with the administration or not of chemotherapy. The survival of the patients that did receive chemotherapy the month before infection was significantly different from patients that did not. Nonetheless, this study has some limitations: our sample is reduced and limited to one center, a bigger cohort will probably result in more consolidated results; our center had few hematologic patients, which might introduce bias to the results.

Conclusion:

Bacteremia is a major cause of mortality and morbidity in cancer patients and currently

there are no guidelines regarding prescription of antimicrobial therapy in cancer patients or in palliative care. Three quarters of the cancer patients that suffer a bacteriemia died in 3

months, and active chemotherapy treatment is associated with lower survival rates. The CTI was the main source of infection.

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Contributors:

FM conceptualized and designed the study.

FM, JM and NJ collected the data.

FM analyzed and interpreted the data.

FM and NB wrote the first draft.

All authors reviewed and commented on drafts of the paper.

[FM - Filipa Macedo, JM - Joana Monteiro, NJ - Neidy Julio, NB - Nuno Bonito]

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