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ORIGINAL ARTICLE

Descriptive analysis of central line-associated bloodstream infections in a pediatric hematology–oncology unit in Montevideo, Uruguay

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Abstract

***Background*:** Central lines are essential for the care of children with cancer.
***Aims*:** To determine the risk factors, characteristics, cost of hospital care, and antibiotic use in pediatric oncology patients with central line-associated bloodstream infections (CLABSIs).
***Methods*:** During 2018–2019, we calculated the rate of CLABSIs in our pediatric hematology–oncology unit.
***Findings*:** Between 2018 and 2019, we detected 34 CLABSIs at our pediatric hematology–oncology unit. We identified neutropenia as the main risk factor for CLABSI (3.74 infections per 1,000 catheter days vs. 1.15 infections per 1,000 catheter days in patients without neutropenia). Three patients died of septic shock. *Escherichia coli*, *Klebsiella* species, and *Pseudomonas* species were frequently isolated. The total healthcare cost of the 34 CLABSIs was more than US$1.2 million.
***Conclusions*:** CLABSI is an avoidable disease among children with cancer. Investing in CLABSI prevention will save lives and financial resources of the hospital. Preventive measures, surveillance, and reporting the rate of CLABSIs are essential for quality assurance and patient safety during cancer-directed treatment of children.

Keywords: *central venous catheter*; *bloodstream infection*; *pediatrics*; *cancer*; *Uruguay*

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Central line-associated bloodstream infections (CLABSIs) are frequent healthcare-associated infections (1, 2), and their rates vary based on the hospital size, the complexity of patient care, the severity of the disease, and the type of central venous catheter used. CLABSI increases the length and cost of a hospital stay (3). Several CLABSI risk factors have been described, including reduced nurse-to-patient ratio, substandard catheter care (e.g. excessive manipulation of the catheter), type of catheter, and the underlying disease that prompted catheter placement (4, 5). According the Centers for Disease Control and Prevention (CDC), the rate of CLABSI is reported as the number of CLABSIs per 1,000 catheter days, adjusting risk based on the number of days the catheter is in use. The surveillance definition for CLABSI includes all blood stream infections (BSIs) that occur in patients with central venous catheters, when other sites of infection have been excluded (2, 6). The microorganisms that most commonly cause BSIs are gram-positive cocci, multidrug-resistant gram-negative bacilli, and fungal pathogens (2).

The incidence of CLABSI can be reduced by adopting best practices in catheter insertion and post placement care, multidisciplinary teamwork, and promoting a culture of patient safety (1, 4). During 2014, the CDC reported a standardized infection ratio of 0.538, with a 50% decrease in CLABSI between 2008 and 2014 (2). Reports of CLABSI rates can be used as benchmarks by individual hospitals to compare their practices to international standards. Professional society guidelines stress the importance of implementing CLABSI bundles (i.e. education and training of staff in charge of central line placement, maintenance, and surveillance) to improve outcomes (1, 7).

Several studies have addressed the incidence and risk factors of CLABSI in the pediatric oncology population, identifying as significant risk factors inpatient settings,

tunneled catheters, and neutropenia (8, 9). Reports from Latin American low- and middle-income countries have also recognized the importance of monitoring CLABSI events according to international classifications (8). In Uruguay, no previous studies have examined the incidence and characteristics of CLABSI in a pediatric hematology–oncology population. Recording our experiences in best practices of the use of central lines is an essential initial step to decrease CLABSIs rates among the children we care for. Therefore, we designed this study to measure the CLABSI rate in our pediatric hematology–oncology unit during 2018 and 2019. We also evaluated CLABSI risk factors, characteristics, cost of hospital care, and antibiotic use.

Methods

Study design and approval

This study was approved by the Pereira Rossell Hospital Ethics Committee, and an informed consent was obtained from all subjects and their caregivers. We included every patient admitted to the pediatric hematology–oncology unit at the Pereira Rossell Hospital, the only referral center for pediatric cancer and stem cell transplantation in Montevideo, Uruguay, from January 1, 2018, to December 31, 2019. At Pereira Rossell Hospital, approximately 100 new cancer cases are diagnosed and treated annually.

The CLABSI bundle we used was aligned to strategies reported in the literature (10) and included education and training of the medical and nursing staff prior to its implementation as well as central line management guidelines, surveillance, and feedback to healthcare staff about the CLABSI rate and its improvement via monthly reports. Our guidelines are built and approved by the staff of the hematology and oncology department, including the procedures for the management of central lines, following international recommendations for pediatric population. These procedures include CLABSI prevention bundles during insertion and maintenance, monitoring, and providing feedback (10–14). These guidelines recommend cefepime as first line therapy for febrile neutropenia and consideration of adding vancomycin if there was a previous MRSA infection or colonization, and in the case of severe sepsis.

Chlorhexidine (2% in solution) was used for skin asepsis during central line insertion and maintenance. Immediately prior to using a catheter, the accessing hub was cleaned with antiseptics, such as a 2% chlorhexidine mixture with 70% alcohol pads. Only sterile needles and syringes were used to access catheters. Dressings were replaced when wet or soiled. Routine dressing changes were done using aseptic technique with clean or sterile gloves. Gauze dressings were changed, and site care was performed with 2% chlorhexidine-based antiseptic every 3 days.

A central line insertion checklist was implemented by the surgical staff. This checklist included essential steps, namely, maximal barrier precautions, including a cap, mask, sterile gown, sterile gloves, and a sterile full-body drape; surgical aseptic technique; skin preparation of insertion site; alcohol-containing skin preparatory agents; insertion; and confirmation of correct insertion. Routine blood samples (biochemistry and blood cell count) were done twice a week; blood cultures, when indicated by febrile neutropenia guidelines, were obtained via the central lines (all lumens). Blood cultures were processed by the laboratory for microbiologic culture studies.

CLABSI data acquisition

The following data were collected at the same time each day by the CLABSI Control and Prevention Team comprising two pediatricians and three nurses: the number of patients admitted to the pediatric hematology–oncology unit and the number of patients with central line infections or CLABSI episodes. Data were uploaded in an Excel (Microsoft Corp., Redmond, WA, USA) file. If a CLABSI was detected, then a dedicated form was completed obtaining facts about the episode, as detailed in Table 1.

We used the CDC/National Healthcare Safety Network (NHSN) CLABSI surveillance definition, which uses mucosal barrier injury (MBI) as a factor in the classification of laboratory-confirmed bloodstream infections (LCBIs) (6). Also, we used definitions that considered the role of neutropenia in the classification of primary LCBIs and MBI LCBIs. The following NHSN classifications were used: LCBI 1, LCBI 2, or LCBI 3; MBI LCBI 1, MBI LCBI 2, or MBI LCBI 3 (6) (Table 1). The corresponding MBI classification applies when the patient is an allogeneic

Table 1. Centers for Disease Control and Prevention surveillance definitions for laboratory-confirmed central line-associated bloodstream infections (6)

Laboratory-confirmed bloodstream infections (LCBIs)	
LCBI 1	A patient of any age with a recognized bacterial or fungal pathogen, not included on the NHSN common commensal list, identified from one or more blood specimens obtained by a culture or non-culture based microbiologic testing methods, and the organism identified in blood is not related to an infection at another site
LCBI 2	A patient of any age with at least one of the following signs or symptoms: fever (temperature >38°C), chills, or hypotension and an organism identified in blood that is not related to an infection at another site, and the same common commensal is identified by a culture or non-culture based microbiologic testing method, from two or more blood specimens collected on separate occasions
LCBI 3	A patient ≤ 1 year of age who has at least one of the following signs or symptoms: fever (temperature >38°C), hypothermia, apnea, or bradycardia, and the same additional criteria as in LCBI 2

NHSN, National Healthcare Safety Network.

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hematopoietic stem cell transplant recipient within the past year with grade III or IV gastrointestinal graft versus host disease, or diarrhea, or the patient is neutropenic. Organisms detected were classified according to the CDC recommendations on commensals or pathogens (6).

Assessments of CLABSI-associated data

The device utilization ratio was defined as the proportion of total patient-days in which central lines were used (number of central line days/number of inpatient days). The CLABSI rate was expressed as the number of CLABSIs per 1,000 catheter-days (number of CLABSIs in the unit/total number of catheter-days in the unit × 1,000). The total number of days in the hospital for each patient with confirmed CLABSI was used to calculate the average length of hospital stay. Risk factors included in this study were neutropenia (absolute neutrophil count <500/mL), concomitant use of total parenteral nutrition (TPN), and blood product transfusions (i.e. the number of transfusions administered before CLABSI was detected).

CLABSI episodes were characterized by primary disease (oncologic or hematologic disease), whether bone marrow transplantation was warranted, the type of central venous catheter (tunneled, implanted, peripherally inserted central catheter; permanent or temporary), the organism identified by blood culture and its susceptibility, antibiotics received, the need to remove the central line, and the overall length of stay.

The cost for the diagnosis and treatment of CLABSI included daily hospitalization cost, either in the regular oncology ward or in the intensive care unit (ICU), the expenses of microbiology diagnostics, and the cost of antibiotics. We calculated the defined daily dose (DDD) of antibiotics and the antibiotic days of therapy (DOT). The DDD of antibiotics was obtained from the hospital pharmacy, and the hospitalization costs were provided by the hospital finance department. We report the antibiotic use measured as antibiotic DOT/1,000 patient days.

For each CLABSI episode, we conducted a similar cost calculation. We reported the costs as median and interquartile range (IQR). The costs were estimated in US dollars (US$), according to historical currency valued by the National Institute of Statistics and Republic National Bank in Uruguay. All statistical analyses were performed using SPSSv.17.0.2 (IBM, Armonk, NY, USA).

Results

We identified 34 episodes of CLABSI in our unit during the study period, representing 4.89 infections/1,000 catheter-days. Most CLABSIs (4.03/1,000 catheter-days) belonged to the category MBI LCBIs; 0.86/1,000 catheter-days were LCBIs (Fig. 1A). The central line days are shown in Fig. 1B. The device utilization ratio was 0.85.

The demographic characteristics and risk factors of the patients with CLABSI are summarized in Table 2 and the identified pathogens in Table 3. Three patients died of severe septic shock; they all had acute lymphoblastic leukemia (ALL) and were undergoing induction treatment. Gram-negative agents (*Pseudomonas* and *Aeromonas* species) were isolated in two patients, and a gram-positive agent (*Bacillus* sp.) was isolated in the other one. Every patient received antibiotics in accordance with local guidelines, for a mean duration of 11.2 ± 1.0 days (range, 2–34 days). *Escherichia coli* was the most frequently isolated bacterium, followed by *Klebsiella* and *Pseudomonas* spp. Four multidrug-resistant bacteria were identified in this study: two methicillin-resistant *Staphylococcus aureus* and two carbapenemase-producing and extended spectrum β-lactamase-producing gram-negative bacteria.

The CLABSI rate for patients who received two or more blood transfusions prior to the episode was 1.73/1,000 catheter-days vs 3.16/1,000 catheter-days for those who received fewer than two transfusions. Referring to the absolute neutrophil count, the CLABSI rate in patients with less than 500/μL was 3.14/1,000 catheter-days, and that for patients with more than 500/μL was 1.15/1,000 catheter-days. No patient was receiving TPN.

During this 2-year period, the mean length of hospital stay of pediatric patients with CLABSI was 21.0 ± 2.6 days (1–60 days). The median cost of hospital stay was US$29,022 (IQR:US$15,880–US$49,120). The median cost of antibiotic treatment for each patient was US$302 (IQR:US$171–US$445). That represents in total (including the cost of each day of the hospital stay plus antibiotics) US$29,409 (IQR:US$16,136–US$49,657). The expenses of microbiology laboratories were not included in the financial burden of the CLABSI. For the 34 episodes of CLABSI, the total hospitalization was 689 days, which represents a total cost of antibiotics of $15,514 and a total cost of hospitalization in the oncology ward and ICU of $1,218,440 (total cost: $1,233,953). Total costs for CLABSI episodes and for each CLABSI episode, including hospitalization, antibiotics, and blood cultures, are shown in Table 4 and the Supplementary Table 1.

Discussion

We report our experience in the quality of practice using vascular catheters at our pediatric hematology–oncology unit in Pereira Rossell Hospital, the only pediatric healthcare center in Uruguay. We conducted a 2-year review of patients who received care therein and the rates, outcomes, and financial burden of CLABSI. We found that not only the CLABSI rate in our unit was higher than those of other developed countries, but also the prevalence of gram-negative organisms causing CLABSI in

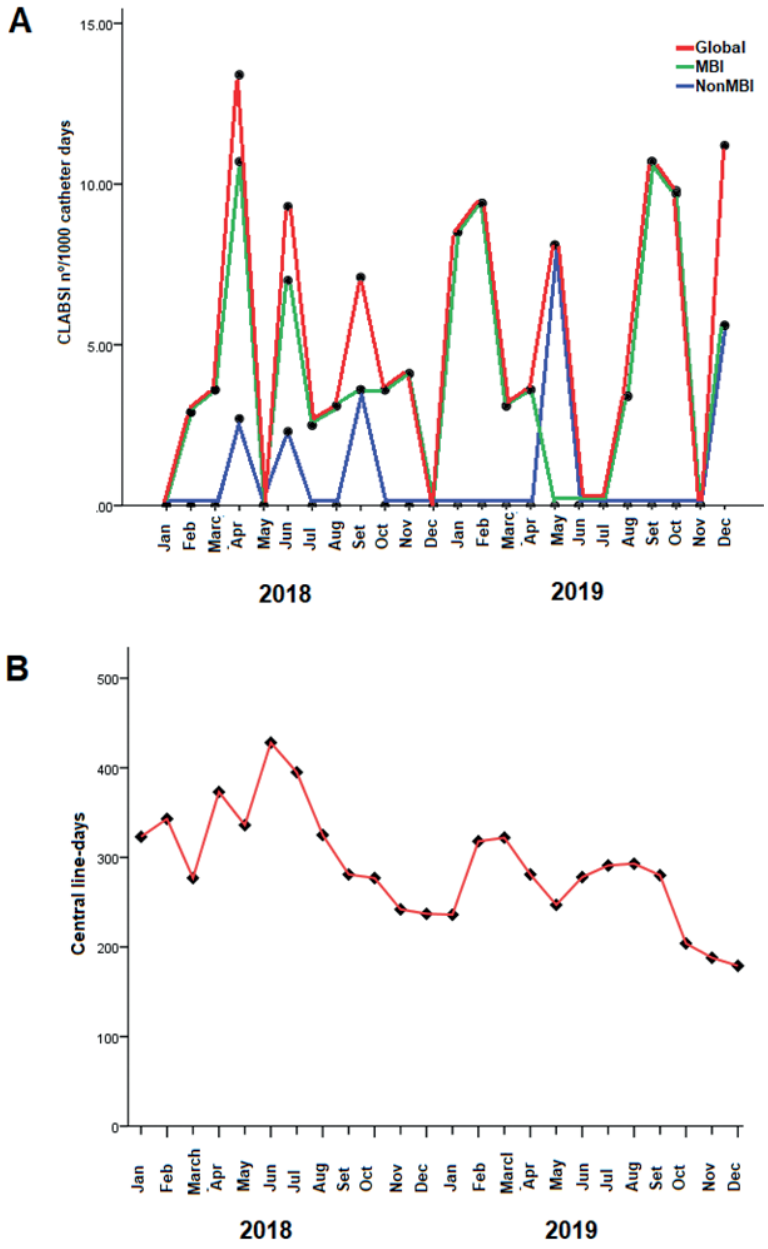

Figure 1. Central line-associated bloodstream infection (CLABSI) rates over a 2-year period in the pediatric hematology–oncology unit at Pereira Rossell Hospital. (A) The global overall CLABSI rate (red plot), that of CLABSIs with mucosal barrier injury (MBI; green plot), and events without mucosal barrier injury (non-MBI; blue plot) are shown. (B) The number of central line days is plotted.

patients with ALL, and the costs related to those episodes were high.

The CLABSI rate at our pediatric hematology–oncology unit was higher than the standard international rate (2). In higher-income countries, a potential reason for lower CLABSI rates is that this measure is used as an indicator of healthcare performance by external agencies during hospital accreditation reviews (15). Another important reason for CLABSI avoidance is to decrease hospital expenditures; insurers, such as the Centers for Medicare and Medicaid Services, do not pay for what they consider avoidable hospital care-associated events (16). These reasons for avoiding CLABSI in higher-income countries, such as the United States, reflect healthcare practices, standardization, and financial gains of different health systems. Adopting these performance inspections will require alignment of institutional practices to healthcare policies and regulations.

The months with the highest CLABSI rates (April–June 2018) were also those with the highest device utilization ratio; these data were consistent with the possibility of increased manipulation of the central line as a

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Table 2. Demographics and risk factors of the 34 pediatric oncology patients who experienced CLABSI

Demographics and risk factors	No. patients[a]	%[a]
Sex		
Female	18	52.9
Male	16	47.1
Primary diagnosis		
B-cell acute lymphoblastic leukemia	26	76.4
Acute myeloid leukemia	3	8.8
Non-Hodgkin lymphoma	2	5.8
Medulloblastoma	1	3.0
Sickle cell disease	1	3.0
Neuroblastoma	1	3.0
Received bone marrow transplantation	4	11.8
Type of central venous catheter		
Implanted	29	85.3
Peripheral indwelling central catheter	2	5.9
Tunneled	3	8.8
Absolute neutrophil count/mL (mean ± SD)	482.9 ± 160.3	
No. blood transfusion before CLABSI (median – IQR)	1	0–2

[a]Data presented are number and (%) unless otherwise indicated. IQR, interquartile range; CLABSI, central line-associated bloodstream infections; SD: standard deviation.

Table 3. Pathogens isolated in CLABSI cases

Pathogens	No. patients[a]	%[a]
Gram-negative organisms	21	61.8
Escherichia coli	9	42.9
Pseudomonas spp.	4	19.0
Klebsiella spp.	4	19.0
Ochrobacteranthropi	2	9.5
Aeromonas spp.	1	4.8
Enterobacter spp.	1	4.8
Gram-positive organisms	10	29.4
Staphylococcus epidermidis	4	40.0
Streptococcus mitis	2	20.0
Staphylococcus aureus	1	10.0
Bacillus spp.	1	10.0
Streptococcus hemolyticus	1	10.0
Staphylococcus hominis	1	10.0
Fungi	3	8.8
Candida parapsilosis	2	5.9
Acremonium spp.	1	2.9

[a]Data presented are number and (%) unless otherwise indicated. spp., species; CLABSI, central line-associated bloodstream infections.

Table 4. Clinical and financial outcomes of CLABSIs

Outcomes	No. patients[a]	%[a]
Classification of CLABSI		
MBI LCBI 1	20	58.8
MBI LCBI 2	8	23.6
LCBI 1	5	14.7
LCBI 2	1	2.9
Central venous catheter removed	11	32.4
PICU LOS, days (mean ± SD)	3	8.8
Total LOS, days (mean ± SD)	21.0 ± 2.6	
Costs	**US dollars**	
Total cost oncology ward	1,173,915	
Total cost PICU	44,525	
Total cost blood cultures	5,700	
Total cost antibiotics	15,514	
Total cost	1,233,953	
DOT (days of therapy/1,000 patient days)	535.6	

[a]Data presented are number and (%) unless otherwise indicated. CLABSI, central line-associated bloodstream infections; MBI, mucosal barrier injury; LCBI, laboratory-confirmed bloodstream infection; SD, standard deviation; PICU, pediatric intensive care unit; LOS, length of stay.

determining factor of the infection rate. A prospective cohort study of neonatal infants has shown that catheter manipulation is a risk factor for infection (15). Therefore, efforts must be made to follow procedures for disinfecting catheter hubs to access them for blood extraction, fluids and medication administration, and other good practices. Compliance with these actions could be enhanced by reminders at point-of-care locations, in the form of checklists of essential practices extracted from guidelines (17, 18). Keeping records of catheter usage by prospective surveillance and periodic reviews of outcomes, especially in high-risk areas, such as an oncology ward or ICU, will establish baseline and threshold rates essential for a unit reference that can be used in quality-improvement initiatives to lower rates of CLABSI (10). Furthermore, prospective surveillance and data review combined with standardization of local practices will help establish catheter usage performance against guidelines for inserting and maintaining central lines.

Catheter-related infections in children with cancer are affected by the inclusion of MBI LCBSIs. Gram-negative bacilli are the most frequently isolated bacteria, according to international data (2). This supports the current febrile neutropenia guidelines in our department, recommending cefepime as the first-line antibiotic in this situation, with a good coverage for both gram-negative (including *Pseudomonas* spp.) and gram-positive bacteria. The majority (82.4%) of episodes in our study were classified as MBI LCBSI, showing that in our unit, CLABSI is documented mostly in neutropenic patients; therefore,

prevention strategies, such as prophylactic antibiotics in patients at high risk of CLABSI, should be considered. Every CLABSI was detected in a patient with a hematologic malignancy, including those whose treatment included bone marrow transplantation. Patients with hematologic malignancies are more susceptible to infections than are patients with solid tumors (1, 7). The majority (85.3%) of patients in this report had leukemia. The CLABSI rate was higher among patients who had received two or more blood transfusions before the episode; however, there was no significant association. In addition, there was no association between the absolute number of neutrophils and CLABSI rates, which probably reflects the small number of patients included in the study. Therefore, a registry of pediatric hematology–oncology cases is needed, so that this association can be analyzed in a larger cohort. The well-established risk factors for CLABSI include the number of blood transfusions, absolute neutrophil count below 500/μL, and TPN (2, 4). No patient in our group was receiving TPN. Most episodes occurred in patients with implantable central lines; nevertheless, this may not be interpreted as a risk factor for CLABSI, as most patients in our unit have this type of device.

Previous studies, both in high- and low-, and medium-income countries, highlighted the same defined risk factors for CLABSI in pediatric hematology oncology units, namely, the presence of neutropenia and the type of central line used (9). In regional studies, the prevalence of MBI LCBI and gram negative agents was also higher (8); further research should focus in identifying measures to reduce this type of events. It might be necessary to consider the potentially modifiable risk factors for MBI LCBI in pediatric oncology patients by concentrating on strategies that could include: the prevention of alimentary tract mucositis, by decreasing the toxicity of some chemotherapeutic regimens, providing low-level laser therapy for oral mucositis, and adhering to excellent and consistent oral hygiene procedures; and enforcing and auditing compliance with central line bundles, and periodically reporting the metrics and updating guidance of catheter use. The benefit of such feedback, as part of routine quality care programs for the care of pediatric oncology patients, has been previously demonstrated (11).

CLABSIs increase costs in different scenarios, like ICU and hematology–oncology units (3, 19). In this study, the average costs of the hospital stay plus antibiotics for each episode were US$36,293. These costs cannot be attributable exclusively to CLABSI episodes, as some patients required admission because of their underlying condition or their oncology phase of treatment. However, reducing CLABSI rates by implementing education, management bundles, and surveillance systems will contribute considerably to lowering infection-related costs (14, 15). More study participants should be included, and more precise methods of billing must be used to estimate the exact cost attributable to CLABSI in the pediatric hematology–oncology population. Like other studies, we did not include physician-related costs, but they should be considered, as they represent approximately 20% of overall costs in many publications (3, 17).

This study has limitations. Although we included all CLABSI episodes in our department prospectively for 2 years, we have no data with which to compare our findings. Nonetheless, this study serves as an initial step toward developing CLABSI surveillance as a permanent task of the Infection Prevention and Control Team in our department, the team will identify problems and propose solutions to decrease the number of CLABSIs. Another limitation is that the data we reviewed for our study were collected for patient care, with the risk of incomplete data. However, in our pediatric oncology unit, the staff members do not rotate to other services, improving the completeness and the quality of recorded information in the patients' chart. Despite this design, our study is foundational for future research. This is a descriptive, non-comparative study with a control group, so a more complete assessment of additional risk factors was not performed. However, an important contribution of our study is that it is the first work from Uruguay to report the number of CLABSIs in a pediatric hematology–oncology unit, and the information could be used as a benchmark to implement interventions to reduce hospital-acquired infections in our setting.

Conclusion

Our findings indicate that most CLABSIs occurred in patients with acute lymphoblastic leukemia and were classified as MBI LCBIs, with a predominance of infections caused by gram-negative bacteria. Given the clear need for permanent surveillance and the report of the rates of CLABSIs in our department, this is the first step to improve patient outcomes and conduct prevention strategies to improve the safety of cancer-directed treatment.

Conflicts of interest and funding

The authors declare no potential conflicts of interest.

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