Predictors of bloodstream infection associated with permanently implantable venous port in solid cancer patients

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Background: The purpose of this study is to characterize the risk factors of bloodstream infection (BSI) associated with the use of permanent implantable venous ports (Port-A) in solid cancer patients.

Methods: Solid cancer patients implanted with a Port-A were prospectively observed for the occurrence of Port-A-associated BSI (PABSI), defined as BSI without other identifiable infection foci. A PABSI risk score was developed using the Cox proportional hazards model.

Results: A total of 415 patients were registered; 88 PABSI episodes occurred in 58 patients (incidence 1.05 per 1000 catheter-days). All but one patient had stage IV cancer. Independent predictors of PABSI occurrence included neutropenia, total parenteral nutrition (TPN), chronic steroid use, invasive procedures, postoperative antibiotics, and preoperative antibiotics. A PABSI risk score with a cut-off value of 0 (sensitivity 88.5%, specificity 64.3%) was defined for stage IV cancer patients as follows: neutropenia, +1.350; TPN, +1.256; chronic steroid use, +1.947; preoperative antibiotics, −0.970; postoperative antibiotics, +0.959; and invasive procedures, +1.098. The median PABSI-free survival was 4.47 months for patients with scores ≥0 but not reached for patients with scores <0 (P < 0.0001).

Conclusion: The PABSI risk score can assist in identifying high-risk solid cancer patients and may assist in designing future preventive strategies.

Key words: Port-A-associated bloodstream infection, risk score, solid cancer

Introduction

Catheter-related bloodstream infections (CRBSI) or catheter-associated bloodstream infections (CABSI) are major causes of morbidity in cancer patients requiring central vascular access for delivery of chemotherapy or other parenteral treatment [1]. Guidelines for the diagnosis, treatment, and prevention of CRBSI have been established [2, 3]. The use of total parenteral nutrition (TPN) and chemotherapy-induced neutropenia were the most frequently reported CRBSI risk factors [4–8].

However, evidence is limited in oncology patients with permanently implantable venous ports (Port-A) who have a reported CRBSI incidence of 0.1–0.2 infections per 1000 catheter-days [2–4]. This patient population represents a minor proportion of patients in previous CRBSI studies, and the CRBSI risk factors in this patient population have not been clarified. With the advance of chemotherapy and supportive care for patients with advanced solid tumors, more comprehensive studies are required to characterize the potential interactions between types and severity of underlying cancers, the types of pathogens, and concomitant treatment on the occurrence of CRBSI and for the development of preventive strategies for high-risk patients.

Diagnosis of CRBSI is based on the culture of the removed catheter tip or on quantitative blood cultures drawn from the catheter and from peripheral veins. These laboratory tests are labor-intensive and cost-inefficient. Port-A catheter removal must consider several factors, including the availability of other vascular access and the severity of the underlying diseases and types of pathogens, and is not always desirable for patients or physicians [9]. The diagnosis of CABSI is commonly used in routine clinical practice (i.e. BSI in patients with an indwelling catheter and no other identifiable infection foci). Because 50%–60% of CABSI in cancer patients is catheter-related (i.e. CRBSI...
CABSI may be a useful surrogate for guiding treatment and prevention strategies. In this study, solid cancer patients with a newly implanted Port-A for anticancer therapy were prospectively observed for the occurrence of Port-A associated BSI (PABSI). The purpose of this study is to characterize PABSI risk factors and to establish a risk score for identifying patients at high risk of PABSI to facilitate future preventive strategy development.

patients and methods

patient population

This prospective, non-comparative study was conducted at a 2200-bed university teaching hospital in Taipei, Taiwan as a continuation of an active surveillance program for health care-associated infection [13]. Solid cancer patients who had a newly implanted Port-A from 1 October 2009 to 31 August 2010 for anticancer therapy in the oncology department of our hospital were enrolled. This study was approved by the Research Ethics Committee of National Taiwan University Hospital, Taipei, Taiwan.

The patients were prospectively observed for the occurrence of BSI until 31 December 2010. The following data were retrieved from their medical records: sex, age, cancer type, and stage (American Joint Committee of Cancer staging system) [14] at the time of Port-A implantation, the use of chemotherapy or TPN, chronic (>1 week) steroid use, neutropenia (white blood cell < 1000/µl or absolute neutrophil count < 500/µl) [15], the presence of significant gastrointestinal (GI) diseases (including prior major GI operation, GI tumor invasion/obstruction, or GI bleeding), and invasive diagnostic/therapeutic interventions following Port-A implantation (including operation, transarterial chemo-embolization, angiography, cardiopulmonary resuscitation, percutaneous nephrostomy, cystoscope, pigtail drainage, pericardial-pleural window, percutaneous transhepatic cholangial drainage), microbiology results of all clinical specimens, and the use of antimicrobial therapy for suspected or documented infections.

Prophylactic antibiotics for Port-A implantation are administered by anesthesiologists or surgeons within 30–60 min before the procedure at the operation room. Beta-iode disinfection followed by the application of whole body drapes is the standard operating procedure for Port-A implantation at the operation room. The types of prophylactic antibiotics are shown in supplementary Table S1, available at Annals of Oncology online. The necessity and selection of postoperative antibiotics were decided according to the physician’s clinical judgment.

Blood cultures were obtained from Port-A and peripheral veins when the patients had clinical symptoms or signs of infection (fever >38°C, chills, fatigue, or leukocytosis). Cultures from other potential infection foci were done to determine the infection origin. Empirical antibiotics were given after blood cultures were taken and adjusted according to culture results. When PABSI is documented, the primary physician determined whether to remove the Port-A based on the PABSI severity, the pathogens identified, and responses to antibiotic treatment.

definition of PABSI

PABSI is defined as one of the following: (i) at least one set of positive blood cultures of recognized pathogens, including Enterobacteriaceae or other Gram-negative bacilli, Staphylococcus aureus, and fungi, without other identifiable infection foci; or (ii) at least two sets of positive blood cultures of bacteria that were potential skin contaminants, including coagulase-negative staphylococci, Propionibacterium species, Bacillus species, or micrococci, together with clinical signs of active infection (fever >38°C, chills, or leukocytosis) [15]. Repeated positive blood cultures with the same pathogen was considered a single episode of PABSI if the two sets of blood cultures were obtained within 1 week (for bacterial pathogens) or within 2 weeks (for fungal pathogens).

Incidence of PABSI was estimated as PABSI episodes per 1000 catheter-days. PABSI-free survival was defined as the duration between Port-A implantation and development of the first PABSI in the case group or last follow-up date in the control group. Overall survival was defined from the Port-A implantation date to death or last follow-up date (whichever occurred first).

statistical analysis and development of PABSI risk scores

We analyzed the risk factors based on a case–control study design. The case cohort consisted of patients who developed PABSI during the study period. For each patient with PABSI, three patients were randomly selected from the same prospective cohort who did not develop PABSI during the study period to develop a control cohort. Cox proportional hazards models were used to identify the risk factors that can independently predict PABSI-free survival and overall survival. The risk factors of PABSI-free survival for different pathogens, including Gram-negative bacteria, Gram-positive bacteria, and fungi, were also analyzed. The variables incorporated in regression analysis are the following: patient age, male percentage, cancer types, cancer stage, the use of chemotherapy or total parenteral nutrition, chronic steroid use, preoperative or postoperative antibiotics administration (defined as the use of antibiotics within 24 h before or after Port-A implantation), the presence of significant GI diseases, and invasive interventions after Port-A implantation. Occasionally, Port-A was implanted soon after a previous infection episode so that pre- or postoperative antibiotics might be part of the treatment course.

A risk score of overall PABSI risk was defined as the summation of the regression coefficients of the independent risk factors from the final Cox regression model. Basic model-fitting techniques for variable selection, assessment of goodness-of-fit, and regression diagnostics were used to ensure the quality of analysis results, as detailed in [16]. Statistical analysis was carried out using R statistical software version 2.6.1 (The R Project for Statistical Computing, http://www.r-project.org/). The performance of the PABSI risk scores was evaluated by the receiver operating characteristic (ROC) plots. Two-tailed P values ≤0.05 were considered statistically significant.

results

patient population

A total of 414 Port-A were newly implanted in 396 patients for anticancer therapy (Figure 1) between October 2009 and August 2010. From the 909 sets of blood culture obtained from 211 patients, 88 PABSI episodes were documented in 58 patients (the case cohort). Blood cultures were obtained from both peripheral blood and Port-A in 64 events (72.7%), only from peripheral blood in 12 events (13.6%), and from Port-A alone in another 12 events (13.6%). Three patients in the case cohort received Port-A implantation twice during the study period. The overall PABSI incidence was 1.05 per 1000 catheter-days (88 PABSI episodes over 83 769 catheter-days). The control cohort included 174 patients randomly selected from the 330 patients without microbiologically documented BSI during the study period. As of 31 December 2010, the median follow-up time was 5.19 months [95% confidence interval (CI) 4.61–6.54 months] for the case cohort and 7.24 months (95% CI 7.06–8.24 months) for the control cohort.
Patients in the case cohort and the control cohort did not differ substantially in age, sex, or cancer type (Table 1). All but one patient in the case cohort had stage IV cancer at the time of Port-A implantation. Patients in the case cohort had a higher incidence of previous BSI including PABSI, significant GI diseases, were subjected to a higher frequency of invasive procedures, and used antibiotics more frequently before and after Port-A implantation. In addition, patients in the case cohort received chemotherapy, TPN, and steroid treatment more commonly and had a significantly higher incidence of chemotherapy-induced neutropenia and mucositis/diarrhea.

The 1-year PABSI-free survival and overall survival in the whole cohort were 80.9% (95% CI 76.0% to 86.1%) and 63.3% (95% CI 57.8% to 69.3%), respectively. The occurrence of PABSI was identified as the only independent predictor for poorer overall survival (HR = 13.11, 95% CI 8.03–21.43, \( P < 0.001 \)) in addition to cancer stage (stage IV versus others, HR = 9.58, 95% CI 2.34–39.29, \( P = 0.002 \)).

Gram-negative bacteria were the most common pathogens (55 episodes), followed by Gram-positive bacteria (35 episodes) and Candida (18 episodes) (Table 2). The occurrence of PABSI caused by Gram-positive bacteria appeared to increase over time after Port-A insertion. However, no statistically significant difference was seen in the median time to PABSI from different pathogens (Table 2).

### Development of PABSI risk score

Because PABSI occurred predominantly in stage IV cancers in our patient cohort, risk factor analysis for PABSI-free survival focused on this sub-population of patients. The Cox proportional hazards model indicates that chronic steroid use, TPN, chemotherapy-induced neutropenia, postoperative antibiotic use, and invasive procedure are significant predictors of PABSI occurrence (Table 3). Conversely, preoperative antibiotic use was identified as a significant protective factor for PABSI.

A risk score for overall PABSI was developed based on the results from the Cox proportional hazards model (Table 3) as follows. The presence or absence of each factor was denoted as 1 or 0, respectively.
The area under the ROC curve of the PABSI risk score was 0.84 (Figure 2A, 95% CI 0.78–0.91, \( P < 0.0001 \)). The cut-off score of \( 0.99 \) yielded a sensitivity of 88.5% and a specificity of 0.91, \( P < 0.0001 \). The cut-off score of \( 0.84 \) (Figure 2A, 95% CI 0.78–0.91, \( P < 0.0001 \)). The cut-off score of \( 0.99 \) yielded a sensitivity of 88.5% and a specificity of 0.91, \( P < 0.0001 \). The cut-off score of \( 0.84 \) (Figure 2A, 95% CI 0.78–0.91, \( P < 0.0001 \)). The cut-off score of \( 0.99 \) yielded a sensitivity of 88.5% and a specificity of 0.91, \( P < 0.0001 \).

PABSI risk score = 1.350 × (neutropenia) + 1.256 × (TPN) + 1.947 × (chronic steroid use) − 0.970 \times \text{(preoperative antibiotic use)} + 0.959 \times \text{(postoperative antibiotic use)} + 1.098 \times \text{(invasive procedure)}.

The area under the ROC curve of the PABSI risk score was 0.84 (Figure 2A, 95% CI 0.78–0.91, \( P < 0.0001 \)). The cut-off score of \( 0.99 \) yielded a sensitivity of 88.5% and a specificity of 0.91, \( P < 0.0001 \). The cut-off score of \( 0.84 \) (Figure 2A, 95% CI 0.78–0.91, \( P < 0.0001 \)). The cut-off score of \( 0.99 \) yielded a sensitivity of 88.5% and a specificity of 0.91, \( P < 0.0001 \). The cut-off score of \( 0.84 \) (Figure 2A, 95% CI 0.78–0.91, \( P < 0.0001 \)). The cut-off score of \( 0.99 \) yielded a sensitivity of 88.5% and a specificity of 0.91, \( P < 0.0001 \). The cut-off score of \( 0.84 \) (Figure 2A, 95% CI 0.78–0.91, \( P < 0.0001 \)). The cut-off score of \( 0.99 \) yielded a sensitivity of 88.5% and a specificity of 0.91, \( P < 0.0001 \). The cut-off score of \( 0.84 \) (Figure 2A, 95% CI 0.78–0.91, \( P < 0.0001 \)). The cut-off score of \( 0.99 \) yielded a sensitivity of 88.5% and a specificity of 0.91, \( P < 0.0001 \).
of 64.3%. The patients were then divided into two groups: low risk (score < 0) and high risk (score ≥ 0). Patients in the high-risk group had significantly shorter PABSI-free survival (median 4.47 months, 95% CI 3.60–8.00 months) than the low-risk group (median PABSI-free survival not reached) (Figure 2B, P < 0.0001).

Predictive factors for PABSI varied by pathogen groups (supplementary Tables S2, S3, and S4, available at Annals of Oncology online). Neutropenia and chronic steroid use were associated with PABSI caused by Gram-negative bacteria and Gram-positive bacteria. Head and neck cancers and invasive procedures were associated with PABSI caused by Gram-positive bacteria. Preoperative antibiotic use was a predictive factor for PABSI caused by Gram-positive bacteria, although not for Gram-negative bacteria or Candida.

discussion

For this study, we examined the clinical characteristics and risk factors of PABSI in patients with advanced solid cancer. The occurrence of PABSI was the most crucial predictive factor for the patients’ overall survival, in addition to cancer stage. The risk scores we developed may assist in the identification of high-risk patient subgroups to facilitate the development of appropriate preventive strategies. We also observed that predictive factors varied by pathogen groups, with Gram-negative bacteria as the predominant pathogen. These findings emphasize the significance of designing preventive strategies tailored to the patients’ clinical characteristics and the targeted pathogens.

Many risk factor analyses have been reported to categorize cancer patients with different BSI risks [17–22]. These studies typically focused on patients with hematological malignancies or patients with neutropenia. Lesser than 20% of patients in our patient cohort had neutropenia. In this study, we identified high-risk sub-populations by incorporating host factors (stage IV disease, cancer types, and neutropenia) and treatment factors (TPN, steroid, antibiotic use, and invasive procedures). The etiologies causing PABSI in this study included Gram-negative bacteria (48.6%) and Candida (17.1%). Because there were no outbreaks caused by these pathogens in the study units during the study period, these pathogens were most likely endogenous flora from the GI tract.

Our data show that PABSI caused by Gram-positive bacteria was associated with invasive procedures. Furthermore, preoperative antibiotic use was a protective factor for PABSI caused by Gram-positive bacteria, but not for Gram-negative bacteria or Candida. Preoperative prophylactic antibiotic treatment has been proven to effectively reduce implant-related infection during orthopedic and cardiovascular surgeries [23–25]. However, the efficacy of prophylactic antibiotics to prevent PABSI is unclear because previous studies have focused on short-term outcomes (infection within 1 mo following Port-A implantation) [26, 27]. These results imply that preventive measures targeting Port-A implantation and long-term bedside aseptic techniques are equally critical for preventing PABSI caused by Gram-positive bacteria. Other preventive strategies for CRBSI or CABS include the use of chlorhexidine disinfectants, antimicrobial-impregnated catheters, and antimicrobial catheter lock solutions [28–31]. The preventive efficacy appears more prominent in reducing skin colonization and decreasing Gram-positive bacterial infection. The optimal preventive strategies to prevent PABSI caused by Gram-negative bacteria or Candida remain undefined.

The use of postoperative antibiotics, which correlated primarily with Gram-negative bacteria PABSI in our models (Table 3 and supplementary Table S2, available at Annals of Oncology online), was more complex. This may imply a concurrent infection episode where treatment was incomplete at the time of Port-A implantation. Thus, postoperative antibiotics use is potentially coincidental with, rather than predictive of, PABSI.

Our study has several limitations. First, the risk score was established from patients with advanced (stage IV) cancer. The major cancer types in this study were GI cancers and lung cancer. Validation of this risk score in patient cohorts of different types of cancers is warranted to clarify the potential interactions between the cancer types, the treatment they received, and the incidence of PABSI by pathogen groups. Second, the incidence and risk factors were defined in this study with CABSI according to CDC definition [32]. This overestimates the incidence of truly catheter-related BSI. The diagnostic values and cost-effectiveness of incorporating dynamic or quantitative cultures into real-life practice, especially the decision-making on catheter removal, should be
evaluated in future clinical studies because of the low rate of positive blood cultures in this patient population (~10% in this study). Third, we selected the control cohort from patients without microbiologically documented BSI, which might include patients with clinical sepsis that has not been verified by positive blood culture.

In conclusion, the occurrence of PABSI is an independent predictive factor for overall survival in solid cancer patients after Port-A implantation. In patients with stage IV cancers, the PABSI risk score we developed may help identify high-risk patients to design optimal preventive strategies.

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disclosure

The authors have declared no conflicts of interest.

references