Augmented Renal Vancomycin Clearance in Cancer Patients: A Case Report and Review of the Literature

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**Established Facts**
- Bacterial infections are frequent in cancer patients and sufficient antibiotic treatment is fundamental in this immunocompromised patient collective.

**Novel Insights**
- Cancer-related increase of renal clearance should be taken into consideration if antibiotic treatment appears to be inefficient.

**Keywords**
Palliative care · Inflammation · Pharmacokinetics · Dose-response relationship, drug

**Summary**

**Background**
Bacterial infections are a major cause of morbidity and mortality in cancer patients. Particularly diagnostic and therapeutic procedures (e.g., central venous catheters, paracentesis) increase the risk of infections in this immunocompromised patient population. In the past, antibiotic therapy was empirically initiated in these patients, guided by treatment regimens designed for patients without malignancy; however, the hyperdynamic circulation in systemic inflammatory response syndrome, as well as the presence of malignancy itself, may have a crucial impact on treatment success. **Case Report:** Here, we report the case of a 55-year-old patient with advanced pancreatic cancer and *Staphylococcus epidermidis* bacteremia who, due to increased renal vancomycin clearance, required treatment with high doses of vancomycin in order to reach therapeutic trough levels. **Conclusion:** Oncological status can be a cofactor of altered pharmacokinetics in terms of a paraneoplastic syndrome. With the help of this case report we want to call attention to this clinically significant phenomenon with its inherent risk of inefficient antibiotic treatment.

**Background**
Bacterial infections are a major cause of life-threatening complications in patients with cancer, either as a consequence of immunocompromising chemotherapy or following diagnostic and therapeutic procedures. In particular, due to the broad application of indwelling catheters and stents, the proportion of infections with Gram-positive micro-organisms has risen over the past decades [1]. When vancomycin (VCM) is administered to oncological patients, in most cases standard dosage regimens are used, although there is evidence suggesting that systemic inflammatory response syndrome (SIRS) or the malignant state may be covariates of phar-
macokinetic (PK) variability. In these cases, standard-dose VCM treatment may often be ineffective, owing to an augmented clearance and distribution volume. However, the underlying mechanisms and effects on PK variability are controversial, especially since data on infection-induced hemodynamic changes in cancer patients are lacking. To highlight these different aspects and to call attention to potentially altered PKs related to malignant tumors, we present here a case of increased VCM clearance in a patient with advanced pancreatic cancer.

Case Presentation

A 55-year-old man was admitted to the Clinic of Gastroenterology and Hepatology at the University Hospital of Cologne due to abdominal discomfort, jaundice and fever. The patient had undergone oncological resection of a pancreatic adenocarcinoma (pT3, pN1, G1) 15 months earlier, followed by adjuvant chemotherapy with gemcitabine. Surveillance imaging had detected hepatic metastases, as well as tumorous cuffing of the celiac trunk and superior mesenteric artery 3 months prior to admission. On admission, physical examination did not show ascites or edema and the Karnofsky index was 80%. Besides insulin-dependent pancreoprive diabetes mellitus, the patient had no other significant past medical history or concomitant medication. A stenosis of the bile duct system was ruled out using abdominal ultrasonography and magnetic resonance cholangiopancreatography (endoscopic retrograde cholangiopancreatography not feasible due to previous duodenopancreatectomy). However, an enlarged aperistaltic intestinal loop was detected bearing the biliodigestive anastomosis and was identified as potential source of infection, the so-called blind-loop syndrome. Blood culture revealed a bacteremia with Staphylococcus epidermidis and Enterococcus faecium, and antibiotic treatment with piperacillin/tazobactam 4.5 g every 8 h together with VCM 1 g every 12 h (30 mg/kg bodyweight) was initiated in accordance with antimicrobial sensitivity testing. Lin/tazobactam 4.5 g every 8 h together with VCM 1 g every 12 h (30 mg/kg BW; jejunal stent placement marked with arrow).

14 days were needed to reach therapeutic trough levels during therapeutic drug monitoring (TDM). Finally, c-reactive protein (CRP) and bilirubin (peak 12.2 mg/dl) dropped and the patient recovered (Fig. 1). 1 month later, the patient was re-admitted with similar complaints. In a subsequent esophago-gastro-jejunoscopy a jejunal stenosis was relieved by enteral stent placement. Fever and bilirubin spontaneously declined, suggesting a superinfection of the afferent loop as the potential source of the initial bacteremia.

Discussion

VCM is a glycopeptide antibiotic that is widely used in the setting of Gram-positive infections. To ensure successful treatment, maintaining adequate plasma levels has to be weighed against the risk of nephrotoxicity; hence, renal function determines the efficacy and safety of VCM treatment. In our case, 2 hypotheses had to be considered in relation to changes in VCM PKs. Recently, Shimamoto et al. demonstrated that a score of SIRS severity was correlated to high creatinine clearance associated with increased VCM-dose requirements (p = 0.01), referred to as augmented renal clearance (ARC) [2]. On the other hand, Baptista et al. observed that ARC was found predominantly in less severely ill patients (mean APACHE II score 14.1 and 19.1 in patients with and without ARC, respectively). Whereas Shimamoto et al. included only patients with preexisting infection, Baptista et al. found ARC to be more likely in patients with trauma but not sepsis as primary indication for admission [3]. Thus, ARC seems to be a phenomenon during the early phase of SIRS/sepsis and vanishes in critically ill patients. Both studies suggest a hyperdynamic circulation characterized by increased renal blood flow with an increase in GFR as an underlying mechanism. No information was given concerning the number of oncological patients in these 2 studies. In our patient, CRP decreased after initiation of high-dose VCM therapy, and the concomitant GFR reduction was most likely caused by VCM nephrotoxicity rather than by inflammation control, since GFR recovered (Fig. 1). During treatment, there were no signs of hyperdynamic circulation, and the patient had a stable heart rate (95% CI, 76.3–85.4/min) and spontaneous blood pressure (95% CI, 114.2–123.7 mmHg), representing a further argument against SIRS-induced ARC.

In the second hypothesis, malignancy itself may have an impact on VCM PKs beyond the altered distribution volume due to edema, peritoneal, or pleural effusion (not present in our patient). In 1995, Chang et al. reported an increase in VCM clearance in pediatric cancer patients using a 2-compartment Bayesian PK method, and this was later confirmed in adult patients with hematological malignancies. According to the authors, oncological patients would need an approximately 50% higher dosage than usual, e.g. 45 mg/kg/day at intervals of 6, 8, or 12 h [4, 5]. In view of the limited and equivocal data for VCM PK studies in this group of patients, caution should be used in adopting these recommendations, especially for the initial dosage. For instance, Omote et al. did not detect a clear difference in the estimated VCM clearance between cancer and non-cancer patients, suggesting dosage adjustment by routine TDM only [6]. Nevertheless, in vivo experiments in tumor-bearing mice argue for such a relationship. In their experiments Shimada et al.

Fig. 1. Course of laboratory parameters.
VCM = vancomycin, GFR = glomerular filtration rate, CRP = c-reactive protein, *treatment with VCM 30 mg/kg bodyweight (BW); **treatment with VCM 45 mg/kg BW; jejunal stent placement marked with arrow.
proposed direct activating effects on renal organic anion/cation transporters (OCT1/2, OATs) by cytokines such as TNF-α, which are indeed increased in the context of cancer [7, 8]. Although the GFR was extremely elevated in our case, it does not seem to be an essential prerequisite for the increase in VCM clearance since 2 series reporting on 155 patients were unable to find a correlation consistent with an active renal VCM transport [6, 9].

Conclusion

Due to the low number of reported cases, it is not possible to draw firm conclusions concerning the cancer type that is preferentially connected to this phenomenon. In summary, there is no sufficient evidence for routinely starting therapy with increased initial VCM dosages in cancer patients. However, cancer-induced changes in VCM PKs should be taken into account in addition to the large inter-individual variability in VCM clearance, warranting TDM and dosage adaption when therapeutic trough levels cannot be achieved.

Disclosure Statement

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References


