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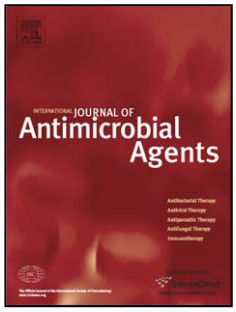

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Empirical first-line treatment with tigecycline for febrile episodes following abdominal surgery in cancer patients

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ABSTRACT

Cancer patients with complicated infections following abdominal surgery represent one of the worst clinical scenarios that is useful for testing the efficacy of empirical antimicrobial therapy. No study so far has evaluated the performance of tigecycline (TIG) when administered as empirical first-line treatment in a homogeneous population of surgical cancer patients with a febrile episode. An observational review of the data records of 24 sequential patients receiving TIG for a febrile episode following a major abdominal procedure in a single cancer institute was performed. Large bowel surgery represented 68% of all procedures, followed by gastric surgery (16%) and urinary–gynaecologic–biliary surgery (16%). Complications following surgery were observed in 68% of febrile episodes, with peritonitis and sepsis accounting for 59% and 24% of complications, respectively. Eight patients needed repeat surgery for source control. The mean duration of TIG treatment was 8 days. Causative pathogens were detected in 16 episodes (64%), and a total of 44 microorganisms were recovered (29% *Escherichia coli*, 9% *Enterococcus faecalis* and 9% coagulase-negative staphylococci). TIG was effective in 12 episodes (48%). The success rate was 67% when infectious episodes sustained by intrinsically resistant bacteria and fungi were excluded. Treatment failure was associated with the presence of complications and with microbiologically documented infection. TIG may be useful as a first-line treatment option in cancer patients requiring antibiotic treatment following surgery when complications are not present or suspected on clinical grounds and when local microbial epidemiology shows a low incidence of primary resistant bacteria.

1. Introduction

Cancer patients may be prone to nosocomial infections as a consequence of chemotherapy or other procedures [1]. Patients affected by solid tumours may also present with post-surgical complications, including peritonitis and sepsis [2]. Intra-abdominal infections (IAIs) remain one of the major challenges facing surgeons and internists because of their associated high rates of morbidity and mortality. Appropriate empirical antibiotic therapy and local nosocomial resistance patterns play a fundamental role in IAIs to improve clinical success rates, reduce length of stay and decrease overall hospitalisation costs [3,4]. Inadequate control of infection, owing to either incomplete drainage or incomplete management of enteric perforation, represents an independent risk factor for treatment failure [5]. Tigecycline (TIG) is a glycylcycline antimicrobial with a broad spectrum of in vitro activity whose use is currently approved for the treatment of complicated IAIs (cIAIs) and complicated skin and skin-structure infections. Empirical therapy with TIG for patients with secondary or tertiary peritonitis would be appropriate as long as *Pseudomonas aeruginosa* or *Proteus* spp. were not a concern owing to its lack of in vitro activity against these isolates [6]. In surgical patients with cancer, for example, risk of infection with *P. aeruginosa* or *Proteus* spp. is associated with additional factors, including mechanical ventilation, prolonged hospital stay or previous exposure to antimicrobial agents [7].

Based on the above considerations, it could be suggested that empirical therapy with TIG in surgical cancer patients might be appropriate if local bacterial epidemiology is compatible with its use and when used upfront at the time of first presentation of abdominal infection. These conditions would minimise the chance of *P. aeruginosa* infection for patients with no previous prolonged antibiotic use.

In addition, in this context there are no studies focusing on patients with solid tumours and febrile episodes following major abdominal procedures.

Here, we studied the clinical performance of TIG in infections associated with abdominal surgery in cancer patients when used upfront as first-line empirical treatment for febrile episodes immediately after surgery.

2. Patients and methods

In this retrospective study, sequential patients with solid tumours who had been treated with TIG for >48 h following febrile episodes occurring after major abdominal procedures between May 2008 and July 2009 at a single institution (Istituto Nazionale per la Ricerca sul Cancro, Genoa, Italy) were considered. Antimicrobial prophylaxis for the prevention of surgical-site infection was administrated according to current guidelines approved by Istituto Nazionale per la Ricerca sul Cancro. Data were derived from clinical records.

Patient inclusion criteria were: established cancer diagnosis; abdominal surgery; febrile episode (≥37.7 °C for ≥6 h) within 72 h after abdominal surgery; and TIG administration within 48 h from onset of a febrile episode. An exclusion criterion was >36–48 h of treatment with other antibiotics.

The following data were collected: demographics (age, sex); hospital ward (High Care, Surgery or Medical Oncology); cancer type and staging; type of surgery; post-surgical complications; use of chemotherapy within 8 weeks before surgery; prior use of antibacterials; microbiological and antibacterial sensitivity data of isolates from blood,

drainage or urine; markers of tissue inflammation and infection [including total leukocyte count and C-reactive protein (CRP)]; and duration of fever.

Data on TIG use, including dose, duration and adverse events, were also collected. Outcome was recorded as response or failure to respond.

All causative microorganisms were identified using routine microbiological methods. Susceptibility testing was performed by the agar dilution method. Disk susceptibility testing was performed and interpreted according to guidelines published by the Clinical and Laboratory Standards Institute (CLSI) [8].

2.1. Definitions

'Response' to treatment was defined as complete resolution of clinical signs and symptoms without therapeutic adjustments.

'Failure' was defined as no significant change in or progression of clinical signs and symptoms during TIG administration, or required change of antimicrobial therapy (e.g. for patients with infections due to organisms resistant to or known not to respond to TIG).

'Complicated infections' were considered as those observed in patients developing post-surgical infectious syndromes including peritonitis and sepsis, or those who needed repeat surgery or invasive procedures for source control (bowel perforation, intestinal occlusion, abdominal abscess, enteric fistula). Patient with a diagnosis of both peritonitis and sepsis were included in the peritonitis group only.

Treatment was defined as empirical when TIG was prescribed for signs of infection without prior identification of a responsible pathogen or even a specific localised source of infection.

Neutropenia was defined as an absolute neutrophil count of <500 cells/μL of blood.

2.2. Statistical analysis

Categorical variables were compared using the χ^2 test. All tests were two-sided, at a significance level of $P = 0.05$. The Mann–Whitney *U*-test was used to compare continuous variables.

3. Results

3.1. Patient characteristics

Within the observation period, 25 febrile episodes meeting the inclusion criteria were identified in 24 patients (13 male and 11 female). Median patient age was 68 years (range 42–87 years). Patient demographics and clinical characteristics are shown in Table 1.

Based on the type of surgical procedure and on the risk of surgical contamination, it was decided to consider separately episodes occurring in patients with gastric surgery (4 patients), urinary–gynaecologic–biliary surgery (4 patients) and large bowel surgery (17 patients).

Seventeen febrile episodes (68%) were sustained by complicated infections, the majority (12 patients) following large bowel surgery. None of the patients had neutropenia immediately before infection or surgery.

Although clinical severity scores [e.g. Acute Physiology and Chronic Health Evaluation (APACHE) score] were not calculated, disease severity in this patient series is relevant and suggested by the presence of advanced malignancy before surgery in 42% of the patients (Table 1) and by the high incidence of complications following surgery (68%), with a high rate of peritonitis and sepsis representing 59% and 24% of complicated febrile episodes, respectively. This compares with only a 20% rate of peritonitis in non-neoplastic patients in other studies [9] and represents a four-fold higher rate.

3.2. Tigecycline use

TIG was given alone as empirical therapy for febrile episodes following surgery in the 25 episodes of infection surveyed. It was administered according to the recommended dosing schedule: an initial dose of 100 mg intravenous (i.v.) followed by 50 mg i.v. every 12 h. The mean duration of TIG treatment was 8 days (range 4–12 days).

In 12 episodes (48%), TIG was replaced by a different regimen owing to either clinical failure or according to antibacterial sensitivity. These regimens consisted of: (i) a broad-spectrum β-lactam with anti-*P. aeruginosa* activity + anti-Gram-positive agent or carbapenem + antifungal agent (fluconazole) (5 patients); (ii) a broad-spectrum β-lactam with anti-*P. aeruginosa* activity + anti-Gram-positive agent or carbapenem + antianaerobic antimicrobial agent (metronidazole or clindamycin) (4 cases); and other antimicrobial combinations (3 patients).

TIG was discontinued in one patient due to increasing liver enzyme serum concentrations.

No other adverse events possibly associated with TIG administration, including nausea, emesis or diarrhoea, were recorded.

3.3. Microbiology

Microbiologically documented infections were observed in 16 febrile episodes (64%), in 11 (69%) of which more than one organism was isolated. In 9 episodes (36%) multiple site cultures yielded no growth of microorganisms.

A total of 44 microorganisms were cultured from blood, urine, surgical wound and drainages. *Escherichia coli* (29%), coagulase-negative staphylococci (CoNS) (9%) and *Enterococcus* spp. (9%) were the most common organisms. *Proteus mirabilis* or *P. aeruginosa* were isolated from two (8%) and three (12%) febrile episodes, respectively. In one episode both bacteria were present. *Candida* spp. was isolated during three febrile episodes (12%). *Serratia* spp., *Klebsiella* spp. and *S. aureus* were recovered in two febrile episodes each, whilst *Streptococcus anginosus*, *Acinetobacter* spp. and *Bacteroides fragilis* were identified in one febrile episode each.

Of the 44 microorganisms isolated, 24 (55%) were isolated in 10 febrile episodes with peritonitis (4 with concomitant bloodstream infection), whilst 12 bacteria (27%) were isolated during 8 febrile episodes with sepsis. Six isolates (14%) were derived from urine in five febrile episodes, eight isolates (18%) were from surgical wound specimens during 5

febrile episodes, and 24 isolates (55%) were derived from 10 peritoneal specimens yielded during 10 febrile episodes.

Analysis of in vitro susceptibility to selected antimicrobial agents with typical activity against the isolated microorganisms is shown in Table 2. Among the Gram-negative isolates, extended-spectrum β-lactamase production was limited (10%), with fluoroquinolone resistance of in six isolates (21%) (Table 2). Forty-five percent of Gram-positive isolates were meticillin resistant but retained sensitivity to glycopeptides and linezolid (not shown).

To provide a quantitative estimate of overall antibiotic resistance, for each microorganism the number of antibiotic agents for which in vitro resistance was observed was evaluated. Indeed, resistance to three or more antibiotics was observed in only 9% of Gram-positive and 6% of Gram-negative isolates, with in vitro susceptibility to all but one antibiotic agent in 73% and 83%, respectively.

3.4. Clinical outcome

Among patients with clinical success, TIG resulted in rapid defervescence (median time to defervescence 1.8 days, range 0–6 days).

A significant correlation was observed between febrile episodes accompanying complicated surgery and microbiologically documented infections ($P < 0.05$) (Table 3).

Overall, when used as single-antibiotic empirical treatment, TIG was effective 48% of times 12 febrile episodes (48%). Improved outcome rates (67%) were observed when

episodes due to microorganisms not susceptible to TIG (i.e. *P. mirabilis*, *P. aeruginosa* or fungi) were not considered.

Absence of infectious complications after surgery, as defined herein, and lack of microbiologically documented infections were predictive of good outcome ($P < 0.05$; χ^2 test). A trend towards higher TIG efficacy was observed when surgical procedures involving the large bowel were excluded (Table 3).

All patients with persistent fever after 7 days of TIG therapy responded to second-line therapy with clinical cure. None of the patients died within 30 days from the beginning of antibiotic treatment.

No associations were observed between the clinical outcome on TIG treatment when accounting for baseline CRP, fibrinogen serum concentrations or neutrophil count.

4. Discussion

Cancer patients with complicated infections following abdominal surgery represent one of the worst clinical scenarios that is useful for testing the efficacy of empirical antimicrobial therapy. This was reflected in this study by an apparently low overall clinical response rate of 48%, which was however improved to 67% when febrile episodes sustained by microorganisms not susceptible to TIG (e.g. *P. aeruginosa*, *Proteus* spp. and *Candida* spp.) were excluded.

These rates differ from previous work [9,10], however relevant differences in the selection of patients, surgical procedures and treatment protocols underlie and explain this apparent

discrepancy. In the pooled analysis of two phase III double-blind trials of TIG versus imipenem/cilastatin in patients with cIAI, systemic malignancy within the prior 6 months or metastatic malignancy to the abdomen within the prior 6 months represented patient exclusion criteria [9]. In an analysis of TIG use in a surgical Intensive Care Unit, only 35 patients had cancer. IAIs accounted for 50% of cases and none of the patients received TIG as empirical monotherapy as other antibiotics were always associated with TIG [10].

In a study of 110 febrile cancer patients with clinical response rates comparable with the present work (overall 64%; 79% in patients with bloodstream infection, 51% in patients with pneumonia) [11], none of the 46 patients with solid tumours underwent surgical procedures and only 9 (8%) of the 110 patients had a cIAI. In addition, treatment protocols differed, as TIG was given as empirical treatment in only 56 patients (51%), with most patients (97%) concomitantly also receiving other antibiotics [11].

The present evaluation therefore has the advantage of reporting a homogeneous group of sequential patients following cancer surgery requiring abdominal procedures. Another possible merit is the possibility of evaluating responses to treatment that are accounted for only by TIG, as other antibiotics were not associated (or switched to) as long as response to first-line treatment was observed.

Significantly higher success rates were observed when peritonitis or sepsis were absent (87%). Patients with such complications had polymicrobial or resistant microbial infections that were more likely to lead to failure of TIG monotherapy and thus a switch to a different antibiotic regimen.

One limitation of the present study is represented by the lack of a control group of patients treated with a different single-agent regimen (e.g. meropenem, piperacillin/tazobactam) to provide an estimate of true comparative efficacy. All patients failing TIG were 'rescued' and cured with a different regimen. The potency or effectiveness of the antibiotic regimen is, however, not a likely issue, as all these 'switch to' regimens included two or more antimicrobial agents and could therefore not be directly compared with a TIG-only regimen.

A high incidence of Gram-negative infections was observed (68%), with *E. coli* (29%) as the prevalent isolate, followed by enterococci (9%) and CoNS (9%). This reflects the origin of infections and is in line with the results from surveillance studies designed to monitor longitudinally the in vitro antimicrobial susceptibility of aerobic and facultatively anaerobic Gram-negative bacilli isolated exclusively from intra-abdominal sites or from sepsis syndromes of abdominal origin [12]. Other studies reported less frequent recovery of *E. coli* and higher frequencies of *Enterococcus* spp. from cases of post-operative peritonitis [13], possibly due to prior antimicrobial use. Recovery of *P. aeruginosa* or *Proteus* spp. in these patients at a rate of 16% is in line with other studies of a similar setting [14,15] and, as expected, affected treatment outcome (i.e. failure). Also the low incidence of episodes with *Candida* spp. (12%) or multidrug-resistant bacterial infections detected here is in agreement with the timing of infection (i.e. early after surgery) and with the absence of prior prolonged antibiotic use. In this regard, use of TIG later after surgery/hospitalisation, and possibly after failure of empirical treatment with different first-line antibiotic regimens, could bear increased risks of failure due to the possibility of selection of emerging *P. aeruginosa* or *Proteus* spp. and of fungi that may determine febrile episodes.

In conclusion, cancer patients undergoing abdominal surgery may be good candidates for early empirical monotherapy with TIG when complications (peritonitis, large bowel perforations) are not present or suspected on clinical grounds and when local microbial epidemiology confirms a low incidence of primary resistant bacteria. Under these conditions and in these patients, TIG represents a suitable alternative regimen to those currently used, thus widening the initial antimicrobial choice.

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Competing interests

None declared.

Ethical approval

Patient treatment was performed according to clinical guidelines for surgical patients. Use of TIG was according to its registered use.

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Table 1

Demographic characteristics of patients

Patient characteristic	Patients [*n* (%)]
Assessable patients	24 (100)
Gender male	13 (54)
Age (years)	
≤65	11 (46)
66–75	6 (25)
>75	7 (29)
Median	68 years
Range	42–87 years
Location of cancer	
Colorectal	15 (63)
Stomach	4 (17)
Ovary	2 (8)
Bladder	1 (4)
Biliary	1 (4)
Mesothelial	1 (4)
Cancer staging	
Metastatic disease at diagnosis	10 (42)
Previous chemotherapy	
<2 months before surgery	4 (17)
≥2 months before surgery	4 (17)

Episode characteristic	Episodes [*n* (%)]
Assessable episodes	25 (100)
Point of care at diagnosis	
ICU	8 (32)
Surgical Unit	15 (60)
Medical Oncology Unit	2 (8)
Type of surgical procedure	
Large bowel	17 (68)
Gastric	4 (16)

Urinary–gynaecologic–biliary	4 (16)
Complications following surgery	
Large bowel	12/17 (71)
Gastric	2/4 (50)
Urinary–gynaecologic–biliary	3/4 (75)
Total	17/25 (68)
Type of complication	
Peritonitis	10/17 (59) [a]
Sepsis	4/17 (24) [b]
New surgery for source control	3/17 (17)

ICU, Intensive Care Unit.

[a] Four patients had concomitant bloodstream infection; four patients needed repeat surgical procedures.

[b] One patient needed repeat surgical procedure.

Table 2

Results of in vitro susceptibility testing of recovered Gram-negative and Gram-positive microorganisms

Antibiotic agent	Resistant isolates [*N* (%)]
Gram-negative isolates	
Amikacin	0 (–)
Carbapenem	1 (3)
Piperacillin/tazobactam	4 (14)
Ceftazidime	5 (17)
Cefepime	3 (10)
Ciprofloxacin	6 (21)
ESBL-positive	3 (10)
Gram-positive isolates	
Oxacillin	5 (45)
Vancomycin	0
Teicoplanin	0
SXT	5 (45)
Rifampicin	1 (9)
Gentamicin	3 (27)

ESBL, extended-spectrum β-lactamase; SXT, trimethoprim/sulfamethoxazole.

Table 3

Clinical response rates in patents treated with tigecycline

Characteristic	Clinical response (%)	Characteristic	Clinical response (%)	*P*-value
Male	57	Female	36	N/S
Age ≤65 years	64	Age >65 years	36	N/S
Large bowel cancer	40	Other tumours	60	N/S
Metastatic disease	45	No metastatic disease	50	N/S
Chemotherapy within 2 months	75	Chemotherapy beyond 2 months	38	N/S
Colorectal surgery	35	Other abdominal surgery	75	N/S
Presence of complications	29	Absence of complications	87	<0.05
TIG start in ICU	25	TIG started outside ICU	59	N/S
Sepsis	50	Peritonitis	30	N/S
Monobacterial infection	33	Polybacterial infection	30	N/S
Microbiologically documented infection	35	No microbiologically documented infection	77	<0.05

N/S, not significant; TIG, tigecycline; ICU, Intensive Care Unit.