Efficacy of extended infusion of β -lactam antibiotics for the treatment of febrile neutropenia in haematologic patients: a randomised, multicentre, open-label, superiority clinical trial (BEATLE)

CURRENT STATUS: UNDER REVISION

Trials BMC

Julia Laporte-Amargos
Hospital Universitari de Bellvitge

Carlota Gudiol

carlotagudiol@gmail.com *Corresponding Author*
ORCID: <https://orcid.org/0000-0003-3095-4422>

Montserrat Arnan
Institut Català d' Oncologia

Pedro Puerta-Alcalde
Hospital Clínic de Barcelona

Francisco Carmona-Torre
Clínica Universitaria de Navarra

Maria Huguet
Hospital Universitari Germans Trias i Pujol

Adaia Albasanz-Puig
Hospital Universitari de Bellvitge

Rocío Parody
Institut Català d' Oncologia

Carolina Garcia-Vidal
Hospital Clínic de Barcelona

José Luis del Pozo
Clínica Universitaria de Navarra

Montserrat Batlle

Institut Catala d' Oncologia

Cristian Tebé

Hospital Universitari de Bellvitge

Raül Rigo-Bonnin

Hospital Universitari de Bellvitge

Carme Muñoz

Institut Catala d' Oncologia

Ariadna Padullés

Hospital Universitari de Bellvitge

Fe Tubau

Hospital Universitari de Bellvitge

Sebastià Videla

Hospital Universitari de Bellvitge

Anna Sureda

Institut Catala d' Oncologia

Jordi Carratalà

Hospital Universitari de Bellvitge

DOI:

10.21203/rs.2.24695/v1

SUBJECT AREAS

Integrative & Complementary Medicine *Internal Medicine*

KEYWORDS

Febrile neutropenia, β -lactam antibiotics, Cefepime, Piperacillin-tazobactam, Meropenem, Extended infusion

Abstract

Background Febrile neutropenia (FN) is a very common complication in patients with haematological malignancies and is associated with considerable morbidity and mortality. Broad-spectrum antipseudomonal β -lactam antibiotics (BLA) are routinely used for the treatment of cancer patients with FN. However, the clinical efficacy of BLA may be diminished in these patients because they present with pathophysiological variations that compromise the pharmacokinetic (PK) parameters of these antibiotics. Optimized administration of BLA in prolonged infusions has demonstrated better clinical outcomes in critically ill patients. However, there is a paucity of data on the usefulness of this strategy in patients with FN. The aim of this study is to test the hypothesis that the administration of BLA would be clinically more effective by extended infusion (EI) than by intermittent infusion (II) in haematologic patients with FN.

Methods A randomised, multicentre, open-label, superiority clinical trial will be performed. Patients with haematological malignancies undergoing chemotherapy or haematopoietic stem cell transplant and who have FN and receive empirical antibiotic therapy with cefepime, piperacillin-tazobactam or meropenem will be randomised (1:1) to receive the antibiotic by EI (during half the time of the dosing interval) in the study group, or by II (30 minutes) in the control group. The primary endpoint will be clinical efficacy, defined as defervescence without modifying the antibiotic treatment administered within the first 5 days of therapy. The primary endpoint will be analysed in the intention-to-treat population. The secondary endpoints will be pharmacokinetic/pharmacodynamic (PK/PD) target achievement, bacteraemia clearance, decrease in C-reactive protein, overall (30-day) case-fatality rate, adverse events and development of a population PK model of the BLA studied.

Discussion Data on the usefulness of BLA administration in patients with FN are scant. Only three clinical studies addressing this issue have been published thus far, with contradictory results.

Moreover, these studies had some methodological flaws that limit the interpretation of their findings. If this randomised, multicentre, phase IV, open-label, superiority clinical trial validates the hypothesis that the administration of BLA is clinically more effective by EI than by II in haematologic patients with FN, then the daily routine management of these high-risk patients could be changed to improve their

outcomes.

Trial registration: European Clinical Trials Database: EudraCT 2018-001476-37

ClinicalTrials.gov Identifier: NCT04233996

Full Text

Due to technical limitations, full-text HTML conversion of this manuscript could not be completed.

However, the manuscript can be downloaded and accessed as a PDF.

Tables

Table 1. BLA adjustment in renal impairment

<i>Creatinine clearance (mL/min)</i>	<i>Dose</i>	<i>Frequency</i>
Piperacillin-tazobactam		
30-40	4 g/0.5 g	Every 8 hours
Cefepime		
30-50	2 g	Every 12 hours
Meropenem		
30-50	1 g	Every 12 hours

Table 2. Participant timeline of the study

Visits	Eligibility visit	Visit 0	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5*	Visit 6
Time points	Admission to NF onset	0	+1 day 12-36 hours	+2 days	+3 days	+4 days	+5 days	+30 ± 3 days
Eligibility screening	✓	✓						
Informed consent	✓							
Personal and clinical data	✓							
Vital signs		✓	✓	✓	✓	✓	✓	✓
Physical examination		✓	✓	✓	✓	✓	✓	✓
Blood test		✓	✓	✓	✓		✓	
PK blood test			✓	✓ (†)	✓ (‡)			
Blood cultures and other cultures		✓						
Blood cultures in case of bacteraemia			✓	✓	✓	✓	✓	
Antibiotic therapy study		✓	✓	✓	✓	✓	✓	
Antimicrobial treatment		✓	✓	✓	✓	✓	✓	✓
Other medications		✓	✓	✓	✓	✓	✓	
Adverse reactions		✓	✓	✓	✓	✓	✓	✓

*: From day 5, daily blood cultures will be performed for any patients with bacteraemia until clearance of bacteraemia.

†: Visit 2 [if not possible, to be done at visit 3 or 4].

‡: Visit 3 [if not possible, to be done at visit 4 or 5, consecutive to visit 2 samples].

Table 3a Sampling time in the intervention group (ABL administration by IE) according to the frequency of administration. Time expressed in minutes from the start of drug administration.

	Frequency of administration	C _{min}	C _{max} (C ₅₀)	C _{max} + 30	C _{max} + 60	C ₇₅
IE	6h	-10	180	210	240	270
	8h	-10	240	270	300	360
	12h	-10	360	390	420	540

Table 3b Sampling time in the control group (ABL administration by II) according to the frequency of administration. Time expressed in minutes from the start of drug administration.

	Frequency of administration	C _{min}	C _{max}	C _{max} + 30	C _{max} + 60	C ₅₀	C ₇₅
II	6h	-10	30	60	90	180	270
	8h	-10	30	60	90	240	360
	12h	-10	30	60	90	360	540

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

[SPIRIT_Fillable-checklist-BEATLE 30.01.20.pdf](#)