Ertapenem administered subcutaneously versus intravenously for urinary tract infections in oncology palliative care patients: a randomized, open, non-inferiority clinical trial

Luciana Ramadas[1], Ianick Souto Martins[2]

1: Infection Control Section, Palliative Care Unit, Brazilian National Cancer Institute José Alencar Gomes da Silva. 2: Infection Control Section, Hospital do Cancer I, Brazilian National Cancer Institute José Alencar Gomes da Silva; School of Medicine, Infection Disease Section, Universidade Federal Fluminense

BACKGROUND

Infections requiring intravenous antimicrobial therapy are very common events in patients with advanced cancer. Nevertheless, these patients frequently present vascular damages becoming extremely difficult to access and maintain intravenous route for hydration and nutritional support. In this context, the subcutaneous route could be implemented as an alternative route for replacement of fluids, electrolytes and drugs. Few studies have evaluated the possibility of using the subcutaneous route for treatment of infections though.

Patients in palliative care often have infections caused by multidrug resistant bacterial such as beta-lactamase producing bacteria. In this context, we hypothesize Ertapenem subcutaneously is not inferior to the same drug intravenously for the treatment of urinary infections in patients on oncologic palliative care, with important advantages such as greater convenience of use.

METHODS

This is a phase 3, randomized open label clinical trial to evaluate Ertapenem administered subcutaneously is non-inferior to the same antibiotic intravenously to treat urinary tract infections in oncological palliative care patients.

The study will be performed at the Palliative Care Unit (PCU) of the National Cancer Institute of Brazil José Alencar Gomes da Silva (INCA), a 56-bed hospital and the only public hospital for cancer palliative care located in the city of Rio de Janeiro, Brazil.

The inclusion criteria are minimum age 18 years-old, any type of cancer in palliative care and urinary tract infection. The exclusion criteria are not assigning the informed consent by patient or legal representative, neutropenia and unconsciousness.

The schedule of procedures includes urine collection for quantitatite culture at baseline as well as urinalysis, and blood for urea, creatinine, albumin, c-reative protein and blood count.

A sample of 82 patients was estimated, considering the level of significance (alpha) of unilateral 2.5%, the power of the study (1-beta) of 80%, the non-inferiority limit of 4%, and success percentages in the groups control and experimental studies of 92% and 100%, respectively. Once the high mortality rate of the study site (about 60%, according to unpublished administrative information), it was decided to increase this number by 30% to compensate for possible losses, totaling 106 patients, 53 in each arm.

Arm	Intervention
Active comparator: Intravenous Ertapenem	Ertapenem 1g/d (if CrCl > 30 mL/min) or 0.5g/d (if CrCl < 30 mL/min). Dilution: 50 mL saline solution. Duration: 30 minutes
Experimental: Subcutaneous Ertapenem	Ertapenem 1g/d (if CrCl > 30 mL/min) or 0.5g/d (if CrCl < 30 mL/min). Dilution: 50 mL saline solution. Duration: 30 minutes

Status: recruiting

Outcomes:

- Primary: microbiological cure in seven days for cystitis and ten to fourteen days for pyelonephritis;
- Secondary: Infusion related adverse events at the end of treatment and clinical response (improve urinary tract symptoms at the end of ertapenem treatment)

Variables: age, gender, weight, height, site of cancer, urinary device , corticosteroid use, renal replacement therapy, albuminemia, creatinine clearance, Palliative Prognostic Score, Karnofsky Performance Status, ertapenem dose , pathogen in urine.

Statistical Analysis: categorical variables will be described through percentage frequencies. Continuous variables will be described by measures of appropriate trends (median or mean) and dispersion. Analyzes of categorical and continuous variables will be performed by chi-square test, Fisher's exact test, Student's t-test or Mann-Whitney test, as appropriate. The active comparator group and the experimental group will be compared for the variables studied to evaluate the randomization ability to distribute the groups equally. Relative risk will be used to measure the association between the intervention and the primary outcome. The level of statistical significance will be 5% and the confidence interval established will be 95%. In multivariate analyzes, the logistic regression model will be used. The outcomes will be analyzed by the intention-to-treat strategy, to ensure initial randomization, and per protocol to ensure data consistency. Efficacy and safety analyzes will be performed every three months from the entry of the first participant, contemplating the occurrence of 25, 50 and 75% of the primary and secondary outcomes.

Ethics Statements: The study was approved by INCA review board, approval number 1.881.308. Clinical Trials Registration: NCT03218800.

Keywords: subcutaneous, ertapenem, urinary tract infection, advanced cancer, palliative.

REFERENCES

INSTITUTO NACIONAL DE CÂNCER. Terapia Subcutânea no Câncer Avançado. Série Cuidados Paliativos. Rio de Janeiro: INCA, 2009.

AZEVEDO, E. F. Administração de antibióticos por via subcutânea: uma revisão integrativa da literatura. Escola de Enfermagem de Ribeirão Preto – USP, Ribeirão Preto, 2011.

INVANZ: ertapenem. WhitehouseStation: Merck Sharp &Dohme, 2007. <https://www.merck.com/product/usa/pi_circulars/i/invanz/invanz_pi.pdf>.

FORESTIER, E. et al. Ertapénem intraveineux ou sous-cutané pour le traitement des infections urinaires à entérobactérie sécrétrice de BLSE. Med Mal Infect, v. 42, n.9, p 440-3, 2012.

PIAGGIO, G. et al. Reporting of noninferiority and equivalence randomized trials. Extension of the CONSORT 2010 statement. Jama, v. 308, n. 24, p. 2594-604, 2012.

TOMERA, K. M. et al. Ertapenem versus Ceftriaxone followed by appropriate oral therapy for treatment of complicated urinary tract infections in adults: results of a prospective, randomized, double-blind multicenter study. Antimicrob Agents Chemother, v. 46, n. 9, p. 2895-900, 2002.

SEALED ENVELOPE LTD. 2012.Power calculator for binaryoutcome non-inferioritytrial. <https://www.sealedenvelope.com/power/binary-noninferior/>

Projeto Gráfico: Setor de Edição e Informação Técnico-Científica / INCA