TWO-TREATMENT COMPARISON BASED ON JOINT EFFICACY AND TOXICITY ORDERED ALTERNATIVES IN CANCER TRIALS

Author's name(s): Letierce A. *, Tubert-Bitter P. 1, Maccario J. 1 and Kramar A. 2

Affiliation(s): 1 INSERM U472, 16 avenue Paul Vaillant Couturier 94807 Villejuif Cedex
2 Centre Régional de Lutte Contre le Cancer, Montpellier

Email: letierce@vjf.inserm.fr
Phone: 01 45 59 50 60 Fax: 01 45 59 51 69

Corresponding author: Letierce A.

Keywords: ordered alternatives, efficacy and toxicity, clinical trial

Topic area of the submission: Multiple Outcomes

Abstract
The primary goal of anticancer treatments is to attain efficacy, however toxicity could affect the course of the therapy. Methods based on the joint distribution for safety and efficacy outcomes have been proposed in phase II [1,2] and in phase III clinical trials [3-5]. These approaches do not take into account the cumulative doses of drugs received by each patient. Moreover, they assume a parametric form for the joint distribution and often use some parameters fixed a priori. Our work deals with the comparison of two treatments. We define a multidimensional parameter based on toxicity and efficacy outcomes and the dose at which one, none or both occur. Each patient is classified into an ordered category depending on the order of occurrence of these two criteria: the sooner the patient benefits from efficacy and/or the later he/she experiences toxicity, the better is the treatment. We then apply likelihood ratio one-sided tests with ordered alternatives. This procedure requires constrained maximum likelihood estimation via isotonic regression [6,7]. A large set of simulations compares the proposed tests to other more usual tests and the results show a good power and a satisfactory type I error control. Our approach is illustrated with a multicenter randomized clinical trial involving patients with metastatic non seminomatous germ cell tumors.
References: