Cancer Treatment Reviews 43 (2016) 50–57

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

Hot Topic

Window of opportunity studies: Do they fulfil our expectations?

Sandra Schmitz [1], François Duhoux [1], Jean-Pascal Machiels *

Institut Roi Albert II, Department of Medical Oncology, Cliniques Universitaires Saint-Luc and Institut de Recherche Clinique et Expérimentale (Pole MIRO), Université catholique de Louvain, Brussels, Belgium

ARTICLE INFO

Article history:
Received 4 November 2015
Received in revised form 21 December 2015
Accepted 22 December 2015

Keywords:
Window of opportunity study
Translational research
Biomarkers
Safety
Breast cancer
Head and neck cancer

ABSTRACT

Window of opportunity studies are trials in which patients receive one or more new compounds between their cancer diagnosis and standard treatment (mainly surgery). Patients are generally cancer treatment naïve. Tumor biopsies before and after the investigational treatment are collected for translational research. Similarly, anatomic and functional pre- and post-treatment imaging may be incorporated. Ideally, the investigational treatment is kept short to avoid delaying standard treatment.

Window of opportunity trials may expedite drug development, improve our understanding of pharmacodynamic parameters, and help to identify biomarkers for better patient selection. They can, however, have major drawbacks including potential safety and logistical issues, delayed standard treatment, and a probable lack of patient benefit. By focusing on breast and head and neck cancers, in this paper we discuss the advantages, disadvantages and design of window of opportunity studies.

Novel cancer treatments are often investigated in unselected end-stage cancer patients [1,2]. The choice of this patient population has, however, important limitations that may impair drug development. First, through previous exposure to anti-cancer treatments, most end-stage patients will have developed multifactorial treatment resistance mechanisms. This may blind the activity of potentially active new agents and prematurely cease their development. Second, the feasibility of conducting translational research to investigate predictive biomarkers and pharmacodynamics is hampered by the ethics of obtaining iterative tumor biopsies in palliative patients. Innovative trial designs that can identify promising new compounds and predictive biomarkers are therefore needed, particularly for targeted agents [1].

The evaluation of compounds in untreated patients prior to standard treatment may resolve some of these issues. Window of opportunity studies are trials in which treatment naïve patients consent to receive one or more new compounds, or a new treatment strategy, in the period between their cancer diagnosis and the delivery of their standard treatment [3,4]. Standard treatment is usually surgery with curative intent (enabling the collection of a substantial amount of treated tumor tissues), but both chemotherapy or radiation-based therapy are plausible. Tumor biopsies are collected before and after the investigational treatment for translational research. Similarly, anatomic and functional pre- and post-treatment imaging can be incorporated.

Excluded from the definition of window of opportunity studies are neoadjuvant treatments or trials in which standard treatment (i.e. chemotherapy and/or radiotherapy) is given with or without an investigational agent with the aim of improving disease outcome [5]. In a neoadjuvant approach, definitive standard treatment (i.e. surgery or (chemo)radiation) is delayed to give the investigational agent time to produce a therapeutic response and improve the overall treatment efficacy.

Marous and colleagues have recently reviewed the designs of preoperative biomarker trials in oncology [6]. They identified 56 trials. The tumor types evaluated included breast cancer (59%), prostate cancer (11%), gastric cancer (5%), non-small cell lung cancer (5%), head and neck cancer (5%), ovarian cancer (4%), pancreatic cancer (4%), gastro-intestinal stromal tumor (2%), and endometrial cancer (2%).

In this review, we discuss the design as well as the advantages and disadvantages of window of opportunity studies in cancer. We illustrate the challenges associated with window studies using examples from breast and head and neck cancer trials.

Window of opportunity studies: design considerations

Fig. 1 depicts the general design of a window of opportunity study. Management issues associated with the trial design should be taken into consideration and include:

* Corresponding author at: Department of Medical Oncology, Cliniques universitaires Saint-Luc, Avenue Hippocrate 10, 1200 Brussels, Belgium. Tel.: +32 (0) 27645457; fax: +32 (0)27645428.
E-mail address: jean-pascal.machiels@uclouvain.be (J.-P. Machiels).
[1] Equal contributors.

http://dx.doi.org/10.1016/j.ctrv.2015.12.005
0305-7372/

a) Duration of treatment

Treatment with the investigational agent must be short, generally a few days or weeks, to avoid delaying curative treatment. Given the risk of disease progression and the potential ineligibility for curative therapy, this point is particularly important. It is even more important if the activity of the compound under investigation is unknown and if there are no postulated or recognized predictive biomarkers.

The treatment duration should also take into account the pharmacokinetic and mechanism(s) of action of the investigated compound. Regarding pharmacokinetics, the drug should be administered enough time to reach steady state to generate meaningful results. Such a period of time might be an issue with drug with a prolonged half-life.

Modulation of phosphoproteins is generally achieved shortly after drug administration if the drug blood levels are appropriate. However, to evaluate gene expression profile, protein expression or immune response, this could require a longer period of time.

b) Timing

The best time to implement a window of opportunity study is during the 'preparation' time between diagnosis and standard treatment. This period is generally used for staging procedures, pre-operative exams, operating theatre reservation, and/or radiation therapy planning. Ideally, patient consent for the study should be obtained early on in the process, sometimes even before the tumor is biopsied, to avoid having to repeat invasive procedures. The trial strategy itself therefore carries a risk of patient loss during the screening process. With head and neck cancer studies, our practice is to therefore discuss window of opportunity clinical trials with the patient at the time of clinical diagnosis [7]. This allows us to prospectively combine standard staging investigations with those required by the window study and avoids the need for certain procedures to be repeated. The acceptable delay between diagnosis and standard treatment is not well defined in the literature, but we consider that definitive treatment should be initiated within four weeks of diagnosis [3,8].

c) Trial endpoint(s)

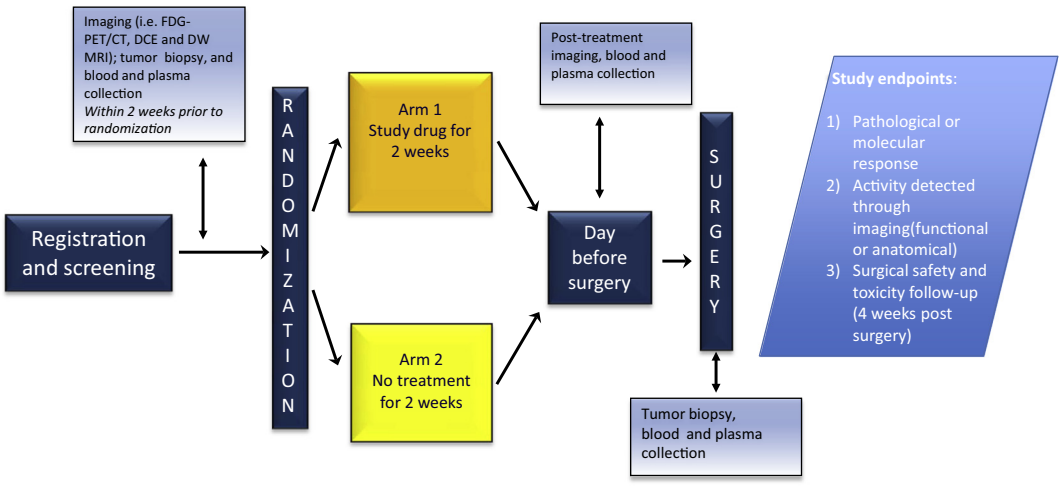
A primary endpoint with a statistical hypothesis to determine the sample size is mandatory. In the Marous' review, the primary endpoint was mentioned in 80% of the study and included pharmacodynamic endpoint in 58%, efficacy in 31%, and safety in 11%. The most frequent pharmacodynamics endpoint was Ki67 (73%). However, information regarding the sample size calculation was present in only 62% of the trials reported [6].

Ideally, although not always feasible, the primary endpoint should be a molecular or a functional imaging parameter that has been validated as a surrogate marker of treatment activity that impacts outcome, such as progression-free survival (PFS) or overall survival (OS). Binary endpoints with a particular cut-off to define responders and non-responders are adequate if the assay used is standardized according to international guidelines and if a particular cut-off has been linked with clinical outcome. However, in case of exploratory analyses, continuous endpoints can also be appropriate.

Ki67 is the most commonly used biomarker of treatment activity in window of opportunity studies. In breast cancer, a change in Ki67 is a validated endpoint linked to treatment efficacy and long-term prognosis [9–11]. However, variability in Ki67 measurement exists and requires standardization, and Ki67 might not be an adequate surrogate marker for all compounds and cancers [12]. Other molecular endpoints, such as a decrease in phosphorylation of the targeted kinase receptor or modulation of some cell cycle regulators, may be good targets for the investigated compound but they also require standardization, validation and central analysis [13–15]. The drawback with proliferative or molecular biomarkers is tumor heterogeneity [12]. A pharmacokinetic sample should be drawn at the time of analysis of the primary endpoint to correlate the biomarker modulation with the drug levels achieved in the blood.

When the primary endpoint is based on a comparison between pre-and post-treatment biopsies, the paired biopsies should be performed under the same conditions and following the same procedures in order to limit the impact of tumor heterogeneity as well as the modifications induced by the procedure itself. In this context, it is probably more appropriate to compare paired biopsies instead of comparing a pre-treatment biopsy with a surgical specimen.

Pathological response, with the quantification of viable residual tumor cells in the surgical specimen, might be linked with long-term outcome and may also offer a valid endpoint [16]. Although



FDG-PET:2-[fluorine-18]-fluoro-2-deoxy-D-glucose positron emission tomography ; MRI: magnetic resonance imaging; DCE: dynamic contrast-enhanced; DW: diffusion weighted

Fig. 1. Typical design of window of opportunity study.