Cancer clinical trials typically have some ‘hard’ endpoints such as death, disease relapse or progression corresponding to scientific objectives of the trial. Hard endpoints are defined as clinical landmarks that are well defined in the study protocol, definitive with respect to the disease process and require no subjectivity (1). Is this definition always acceptable?

Suppose there is no ‘lost to follow-up’ in long-term cancer clinical studies. If death from cancer is a study endpoint, it always has been and still is controversial whether we should treat death by an obvious accident after solid evidence of disease progression as an event or as a censoring. Moreover, in the case when disease progression is selected as a study endpoint, it is also not easy to define the data handling methodology for patients who died from cancer without obvious evidence of disease progression. Even if we plan to conduct clinical trials based on ‘hard’ endpoints, there are many data handling methods and much room for introducing a potential bias into the trial by the selected methods. Therefore, the total validity of the analysis should be guaranteed by determining the methodology of the data handling that takes various characteristics and progression of the disease into consideration. It is also critical to determine and describe precisely in a protocol or in a statistical analysis plan what type of data handling methodology will be applied in the clinical trial before the start of the trial. Advance description of the detailed planning of data handling and analysis has now become compulsory to raise the credibility of a clinical trial.

On the other hand, in clinical studies for chronic disease such as cancer, a long-term follow-up of the patients should be necessary throughout the trial. No matter how we select the sound data handling method, there is still much room for producing biased estimates of measures such as survival and time to progression by non-compliance with a pre-specified follow-up schedule.

In this regard, it is of practical interest and importance that Niimi et al. (2) shed light on the significance of periodic and accurate observations in clinical trials by using data from their actual studies. As stated by the authors, it is fundamentally impossible to restore missing information from incomplete observation at the stage of data analysis. The gist of this statement is that it is also persuadable that any type of analytical methodology to compensate for insufficient information has its advantages and disadvantages and, to date, no standard method to cover all those circumstances has been universally accepted.

In Niimi et al.’s paper, three different analytical methods (METHOD-A, a method using as much event data as possible from the collected data; METHOD-C, the idea that only reliable data should be adopted; and METHOD-B, an intermediate method between METHOD-A and METHOD-C), to cope with missing information regarding disease progression were compared. First, it seems that the difference between METHOD-A and METHOD-B rests in the objective of study, i.e. the definition of the study endpoint. In METHOD-A, death occurring by causes other than primary disease was treated as an event, whereas in METHOD-B it was handled as a censoring. The decision to adopt either one of these two methods depends mainly on the study endpoints selected for more appropriate evaluation of the difference in effectiveness between treatment arms.

METHOD-C is a totally different approach to the other two methods because all information after a last visit or examination is ignored even if we obtain reliable or unreliable information about patient outcomes. This might be the most unbiased estimation in terms of the independence from the information after the last periodic observation. However, it could also be true that this estimation may turn out to be invalid at the time point when an investigator later obtained solid information on the patient outcomes. If the investigator is informed of death by the primary disease in a patient, it is not always appropriate to treat that case as censored at the last examination time, because this ‘informative censoring’ might lead to other seriously biased results of the study. For example, if an investigator deliberately stops periodic observation of high-risk patients who have no evidence of disease progression, they will all be considered as censored cases regardless of the outcomes of the disease. In such circumstances where an investigator is able to control intentionally the result of a clinical trial, statistical compensation is almost impossible.

To obtain more accurate estimates of time to progression, it is essential to minimize the number of the patients who are missed regarding disease progression, by shortening the interval between observations and collecting accurate, high-quality data. However, such attempts have certain limitations. To handle such data more accurately, more advanced methodologies

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such as an interval-censored approach, assuming the occurrence of events within an interval of time, might be of practical significance. Although a number of statistical investigations have been performed (3,4), few reports on actual data from clinical trials have been published to date (5). Further investigations are necessary to determine the most appropriate data handling methodology in various types of clinical trials.

References