Endpoints in oncology clinical trials

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Summary

In oncology clinical trials, many different endpoints can be used as primary or secondary endpoints. Advances in cancer treatment have provided longer survival outcomes, particularly in certain types of cancer. Overall survival is accepted as the gold standard endpoint for demonstrating clinical benefit; however, it is associated with some disadvantages such as requirement of long-term follow-up, requirement of higher number of patients, and high cost. Thus, the question "what is the most appropriate endpoint in clinical trials?" comes to mind. The present review discusses the endpoints in oncology clinical trials.

Key words: *clinical studies, oncology, progression-free survival, surrogate endpoints, survival*

Introduction

In cancer treatment, targeted therapies following chemotherapy and use of immunotherapeutic agents in recent times have provided longer survival outcomes, particularly in certain types of cancer. In addition to the positive developments such as high response rates and long survival obtained particularly with targeted agents, high treatment costs also cause changes in the assessment and interpretation of clinical trials. Considering factors such as overall survival (OS) and long-term tumor response despite of the failure in progression-free survival (PFS) in the studies with immunotherapeutic agents, the question "what is the most appropriate endpoint in clinical trials?" comes to mind. The present review discusses the endpoints in oncology clinical trials.

Clinical trials and endpoints

In oncology clinical trials, many different endpoints can be used as primary or secondary endpoints. Numerous endpoints such as OS, objective response rate (ORR), disease-free survival (DFS), PFS, and quality of life (QoL) are preferred in clinical trials. While OS and QoL are classified as patient-centered endpoints, others are classified as tumor-centered endpoints [1-4]. Each of these

endpoints is preferred for different purposes in different studies. Choosing a wrong endpoint makes the study outcomes debatable. In particular, a quick and long-lasting response obtained with some targeted therapeutic agents in recent times leads researchers to prefer different endpoints. Hence, the variety of endpoints in recent clinical trials performed with the drugs approved by the Food and Drug Administration (FDA) attracts attention (Figure 1). While survival was the primary endpoint in 30% of overall trials conducted with the FDA-approved cancer drugs between 1990 and 1999, this rate decreased to 14.5% in the clinical trials conducted between 2006 and 2011 [5]. With the use of numerous targeted therapeutic agents and considering relevant studies, this rate is expected to further decrease after 2015.

Along with the use of radiological examination in the early 1970s, the FDA used to approve the drugs based on the ORR in oncology studies. Thereafter, however, also considering the recommendation of Oncologic Drugs Advisory Committee, it was concluded that drug approval should be performed based on OS and QoL, the endpoints that represent the evidence of clinical benefit. However, OS cannot always be predicted by ORR and thereby it is not appropriate for every study.

Various factors need to be taken into account while specifying the endpoints. Some of these factors include cancer types, histological subgroups, the study being performed on adjuvant or metastatic setting, treatment step, life expectancy, and basic requirements of regulation.

Disease-free survival

DFS is defined as the time to the development of new disease following complete radiological resolution of tumor after curative treatment with surgery, radiotherapy or chemoradiotherapy. PFS is defined as the time to the progression of already existing lesion or to the development of new lesion from the initiation of treatment in locally advanced-stage or metastatic disease. OS is defined as the time to the patient's death from diagnosis or from the initiation of relevant treatment. ORR is defined as the total number of patients with partial and objective response obtained by treatment of the tumor.

A good endpoint should have certain features. Primarily, a good endpoint should be clinically relevant and beneficial. Besides, it should be effectively measurable particularly using an appropriate scale, sensitive and specific, of low-cost, and reproducible. For this reason, different endpoints could be preferred in different disease groups or in the adjuvant therapy lines of a disease and in the treatment lines of metastatic stages of the same disease, and sometimes more than one endpoint (as primary and secondary endpoints) can be used. Table 1 summarizes advantages and disadvantages of endpoints in oncology trials.

Overall survival

The primary goal of the treatment of cancer patients is to provide cure. For this reason, OS is the most important endpoint in oncology clinical
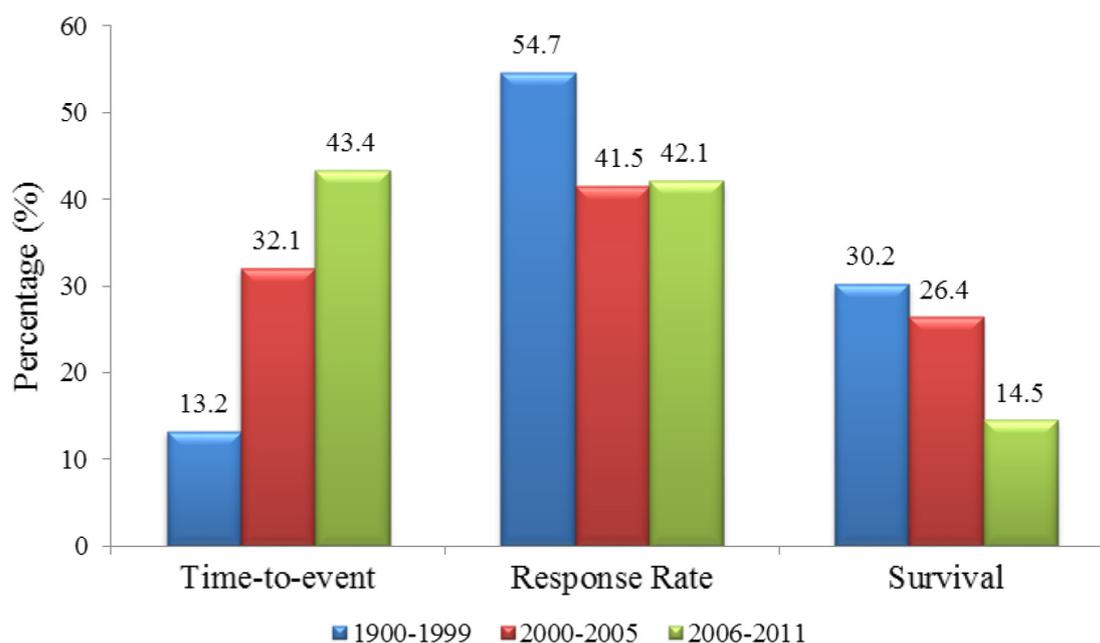

Figure 1. Distribution of the FDA-approved drugs through the years.

trials and is the gold standard for demonstrating clinical benefit. OS is a patient-centered endpoint. Other endpoints are known as surrogate markers and are named as tumor-centered endpoints. While the FDA deemed tumor response rate, which is a surrogate marker sufficient for drug approval until 1980s, OS has begun to be used for drug approval since 1985 [6]. Based on non-survival endpoints for cancer drugs, the FDA has started to use regular or accelerated approvals [6]. OS is defined as the time from randomization to death and is the most ideal endpoint. It is easy to measure and the outcome is definite as there is no doubt that the event has happened [7]. Subjective evaluation or researcher bias is unlikely to occur [8]. Therefore, as an endpoint, it does not lead to mistakes. OS definitely indicates the clinical benefit; therefore, it is the most appropriate endpoint to be preferred in oncology trials. Although OS appears to be the most ideal endpoint, it has some disadvantages. In particular, requirement of long-term follow-up and thereby requirement of higher number of patients are among the leading problems [9]. These two factors cause the studies using OS as an endpoint to be the ones of much higher cost. Number of patients and cost are critical problems particularly in patient groups with slow clinical progression and requiring long-term follow-up. OS is usually measured in the intention-to-treat population [7]. Using OS as an endpoint is not applicable in slowly progressive diseases with long expected survival such as hormone receptor-positive breast cancer and

Table 1. Advantages and disadvantages of endpoints in oncology trials

Endpoint	Approval	Advantage	Disadvantage
Overall survival	Clinical benefit for regular approval	• Directly measures clinical benefit • Easily measurable • Gives definite results	• Requires quite high patient number • Influenced by cross-over and subsequent therapies • Influenced by non-cancer deaths
Progression-free survival	A surrogate marker for regular and accelerated approval	• Requires limited patient number • Requires short follow-up period • Not influenced by cross-overs or subsequent therapies • Requires objective and quantitative evaluation	• It cannot be statistically validated that it is a surrogate marker for survival • Not definitely measurable • Evaluation is subject-dependent with high risk of bias • Definitions may differ between studies • Time of evaluation needs to be balanced between treatment arms
Disease-free survival	A surrogate marker for regular and accelerated approval	• Requires limited patient number • Requires short follow-up	• It cannot be statistically validated that it is a surrogate marker for survival • Not definitely measurable • Definitions may differ between studies
Objective response rate	A surrogate marker for regular and accelerated approval	• Needs to be evaluated in single-arm studies • Much quicker evaluation as compared with survival studies • Requires much more limited patient number	• Benefit cannot be measured directly • Detailed measurement of drug activity is unavailable
Quality of life	Clinical benefit for regular approval	• Able to directly measure the patient's benefit	• Data may frequently be missing and inadequate • Clinical relevance of very small changes is unknown • Requires multiple analyses • Requires validation

low- or moderate-stage neuroendocrine tumors. In such tumors, treatment in the further steps, particularly treatments with targeted agents or, as in the example of breast cancer, sequential use of other hormonotherapy agents, and cross-overs have substantial effects on OS. Hence, study drug-associated OS benefit could not be demonstrated in the great majority of clinical trials conducted in patients with breast cancer receiving adjuvant hormonotherapy. Likewise, change in OS may not be observed due to sequential use of targeted agents and cross-overs, i.e. using targeted agent later in the other study arm. Among 58 randomized clinical trials conducted in patients with advanced-stage breast cancer, OS was used as an endpoint in only one study, suggesting that the endpoints giving results in a shorter time have started to be preferred [10]. Comparison of differences in OS is quite difficult in drug studies on the first-line treatment of patients with metastatic breast cancer due to subsequent therapies and long-term survival expectancy [11]. Another important point is that a drug becomes outmoded before showing its efficacy due to discovery of new tumor pathways, targets, and molecules in numerous types of cancer until obtaining the outcomes of the studies designed to determine OS.

Progression-free survival

Recently, PFS is one of the most commonly preferred endpoints in oncology clinical trials. PFS is used because it frequently provides direct information about drug activity [12]. It is easy to measure PFS; however, it could be debatable whether PFS is a correct endpoint or not since prolonged PFS does not always contribute to the extension of survival. Although the fact that PFS can be defined easily and appears to be its major advantage, its relevance for patients is questionable in the event that survival is not prolonged. Particularly, the effects of other therapeutic agents, which are used after the development of progression, on survival limit PFS's being a good endpoint in real terms. There are many reasons for PFS to be preferred as an endpoint. The fact that progression appears earlier and more frequently as compared with death leads to finalization of clinical trials in a shorter time and thereby completion of the clinical trials with less number of patients and accordingly reduced cost [8,13]. Not being influenced by post-progression therapies is also another reason for PFS to be preferred by the sponsors because this indicates the efficacy of drug. Today, however, the benefit of PFS could not be demonstrated in immunotherapy studies, in which numerous clinical trials are still be-

ing carried out, since it usually takes nearly 10-12 weeks from the activation of T cells to the appearance of cytotoxic features. Nevertheless, clinical benefit in OS and long-term response are obtained in this group of drugs despite the absence of PFS benefit. All of these reasons indicate that PFS is by no means appropriate and preferable endpoint for immunotherapy studies although it has been frequently preferred as an endpoint in the earlier clinical studies.

Since PFS can be determined in a short time and studies using PFS as an endpoint are associated with low cost as compared with those using OS as an endpoint, it is debatable whether PFS can be used as a surrogate marker instead of OS. Therefore, this has been investigated for certain types of cancer, and the FDA accepted in 1991 that PFS could be used as an endpoint instead of OS due to the fact that PFS benefit obtained for colorectal cancer and ovarian cancer could predict OS benefit. However, it is not the predictor of OS in diseases such as breast cancer and prostate cancer, which are hormone-dependent and relatively slowly progressive with long-term survival expectancy. It is thought that the efficacy of therapies used after progression is particularly the main reason for failing to demonstrate OS benefit in slowly progressive diseases with long-term survival expectancy. The FDA anticipates that PFS may be a more accurate endpoint as compared with ORR for the evaluation of stable disease [13]. PFS is increasingly being used as the primary endpoint because of quite low OS benefit obtained in numerous clinical studies evaluating the patients with advanced-stage breast cancer [14]. The fact that PFS can be determined in a shorter time as compared with OS suggests that it can be used as a surrogate marker instead of OS [9]. However, improvement in PFS is not always sufficient in predicting a better OS outcome [15].

Although PFS and time to progression (TTP) are quite similar endpoints, they are different in some respects. While PFS indicates the time from randomization to disease progression or death, death is not considered as an event while evaluating TTP. For this reason, PFS can better represent OS and the FDA prefers PFS rather than TTP [16]. Today, it has been propounded that PFS is a surrogate marker instead of OS in cases with advanced-stage colorectal cancer [17,18].

Disease-free survival

DFS, which is also called as recurrence-free survival, is an endpoint similar to PFS. While PFS is an endpoint used in locally advanced or metastatic diseases for which curative treatment op-

tions could usually not be implemented, DFS is used in clinical trials in which the benefit of adjuvant therapy is evaluated in patients with no sign of disease following curative treatment [13]. DFS better reflects OS in patient groups with long-term survival expectancy and studies using DFS as an endpoint are low-cost and completed in a shorter time similar to those using PFS as an endpoint [13]. However, DFS benefit usually does not reflect OS benefit in the relatively slowly progressive tumors with long-term survival expectancy such as hormone receptor-positive breast cancer. Such trials need to have longer follow-up period and to be performed in higher number of patients to reflect OS benefit. In 1990, the FDA accepted DFS as an endpoint for adjuvant treatment of node-negative breast cancer and colon cancer [13,19,20].

Objective response rate

ORR rate is an endpoint occasionally used in oncology clinical trials; however, its benefit is a matter of debate. As spontaneous remissions of tumors are quite uncommon, ORR reflects antitumor activity and is used as an endpoint. ORR is usually defined as the sum of complete and partial response rates [13]. Obtaining the results in 2-3 months makes it preferable particularly for accelerated approval of drugs [21]. The fact it does not yield OS or PFS benefit despite tumor regression is a critical problem. However, it might be a significant surrogate marker if PFS and/or OS benefit could be obtained in patients with high ORR. Moreover, ORR can be used to show the efficacy of targeted therapeutic agents, particularly in certain diseases. While the ORR obtained with chemotherapy in patients with BRAF-mutant metastatic melanoma is approximately 10%, BRAF inhibitors provide an ORR of 50%. This is important because it involves also PFS. The rate is higher and PFS benefit is longer with the combination of BRAF inhibitor and MEK inhibitor. Likewise, in patients with anaplastic lymphoma kinase (ALK) mutation, a much higher ORR is obtained with ALK inhibitors than with chemotherapy. This might be predictive for PFS and OS benefit. For this reason, high ORR in early period may be a good endpoint for such group of drugs. In general, however, it is obvious that ORR is not as an effective endpoint as PFS or OS. ORR is preferred as the primary endpoint for accelerated FDA approval in cancer types for which such type of targeted drugs are used, particularly in some selected cancers. Moreover, ORR is used in refractory cancer types for which there is no or limited therapeutic options and the treatment response is poor.

ORR is a quite better endpoint for neoadjuvant therapies and is preferred frequently. Efficacy of therapies used before curative treatment provides both implementation of a better curative therapy and can usually reflect other endpoints such as PFS and OS. However, although ORR, particularly complete response rate, is an endpoint frequently used in studies on neoadjuvant therapy in breast cancer patients, it remains inadequate in reflecting the endpoints such as PFS, DFS and OS that are better indicators of clinical benefit. The primary reason for this is the direct contribution of therapeutic options used after curative treatment to these endpoints.

Pathological complete response

Pathological complete response (pCR) is an endpoint especially used in neoadjuvant studies. pCR is of importance as it directly indicates the decrease in tumor diameter. pCR can demonstrate clinical benefit in a much shorter time particularly in high-risk populations. pCR is particularly used in accelerated drug approvals. It is approved by the FDA as a beneficial endpoint in early-stage breast cancer patients [22]. While it is able to directly show drug activity in patients appropriate for surgery, the results cannot go beyond being debatable in patients not benefiting from treatment or not appropriate for surgery.

Quality of life

Quality of life, which is a patient-centered endpoint, is not a frequently preferred endpoint for efficacy in oncology patients. QoL should be preferred in studies evaluating favorable effects of palliative therapeutic agents, or the agents considered to have similar effect on toxicity and QoL. Nevertheless, QoL is generally preferred as a secondary endpoint in oncology clinical trials. QoL is accepted as an endpoint by the FDA as it indicates clinical benefit [13,21].

Other endpoints

In addition to the above-mentioned endpoints used frequently in oncology clinical trials, there are also some rarely used endpoints. However, these endpoints become prominent rather in the studies funded by the sponsor companies. The two of these endpoints are depth of response and early tumor shrinkage. Both endpoints have been suggested to reflect longer survival outcomes (PFS and OS) in patients with metastatic colorectal cancer. Nevertheless, the use of these endpoints in studies performed neither with colorectal cancer nor with the other types of cancer has been accepted. De-

crease in tumor diameter has been demonstrated to be associated with better OS outcomes in colorectal cancer patients with hepatic metastasis [23].

Conclusion

Overall survival is the gold standard endpoint in oncology clinical trials. However, due to the OS-associated disadvantages such as requirement of long follow-up periods, requirement of higher number of patients, and high cost, other endpoints that are able to predict OS are used. An endpoint needs to be selected considering multiple factors such as cancer type, stage, purpose of treatment, and expected duration of survival for the relevant disease.

Conflict of interests

The authors declare no conflict of interests.

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