The Maemondo Paper: Understanding Outcomes Assessment in Clinical Trials

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Authors' disclosures of potential conflict of interest are found at the end of this article.

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The goal of any clinical research evaluating a new cancer therapy is to determine if the treatment provides clinically meaningful benefit and is safe (Fleming, 2006). A randomized controlled clinical trial is the primary vehicle used in oncology to compare a novel treatment to an established standard of care (Shi & Sargent, 2009). The impact of the novel treatment compared to the established standard on overall survival (OS) is considered the "gold standard" in evaluating the effectiveness of a treatment. However, the use of OS as the primary endpoint has several limitations, including cost, the length of time required to complete a study, and the inability to take into account the impact of subsequent therapies on OS in the patient group (Fleming, 2005, 2006; Schatzkin, 2000).

Surrogate Endpoints

The use of surrogate endpoints has been employed so that outcomes can be determined sooner or more frequently and at less cost. These outcomes may improve or expedite the drug approval process, enhance the feasibility of trials, and potentially make the experimental therapy available to patients more rapidly, which may improve quality and length of life for individuals with cancer (Fleming & DeMets, 1996; Shi & Sargent, 2009). A published definition of a surrogate endpoint of a clinical trial is, "a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that directly measures how a patient feels, functions, or survives and is thought to be an adequate substitute for the gold standard (typically OS)"

(Shi & Sargent, 2009, page 103). Surrogate endpoints commonly used in the evaluation of cancer therapies include tumor response rate (TRR), such as complete and partial response rates (CR and PR), time to progression (TTP), progression-free survival (PFS), and disease-free survival (DFS). Table 1 includes the definition of each of these measures.

Impact on these surrogate endpoints is expected to reflect changes that would occur if the gold standard were used (Hughes, 2008). However, there is the potential that an improvement in a surrogate marker may not predict improvement in the gold standard. For example, if the toxicity of a drug significantly reduces quality of life, the meaningful benefit of a treatment may be questioned even if PFS is improved. In addition, a drug may result in decreased time from progression to death, even if PFS is improved through unintended mechanisms that impact tumor growth or other mechanisms unrelated to growth of the tumor, such as other organ toxicity (Fleming, Rothmann, & Lu, 2009).

In oncology, more than half of the anticancer drug approvals were based on endpoints other than the gold standard (OS), and between 1990 and 2004, over two thirds received regular approval, not just accelerated approval requiring further testing (Shi & Sargent, 2009). However, limitations of surrogate endpoints have been reported. For example, response rate has been unreliable in predicting OS in a variety of cancers (Hackshaw, Knight, Barrett-Lee, & Leonard, 2005; Shi & Sargent, 2009; Tang, Bentzen, Chen, & Siu, 2007). Disease-free survival has demonstrated validity as a surrogate for OS in specific cancers, including adjuvant therapy for colon cancer (Burzykowski, Buyse, Yothers, Sakamoto, & Sargent, 2008a; Sargent et al., 2007; Sargent et al., 2005). Progression-free survival has shown strong surrogacy for OS (Buyse et al., 2007; Shi & Sargent, 2009) in metastatic colon cancer, but not in advanced breast cancer (Burzykowski et al., 2008b; Miksad et al., 2008).

Progression-Free Survival

The North-East Japan Study Group trial reviewed by Karen Oishi used PFS as a surrogate endpoint to evaluate the impact of the experimental therapy. Progression-free survival is defined as the time to the detection of progressive disease or death (Fleming et al., 2009). Important characteristics of PFS are that it directly measures the effect of treatment on the tumor burden process,

Table 1. Definitions of Endpoints of Response

Endpoint	Definition
Overall survival (OS) rate	The percentage of people in a study or treatment group who are alive for a certain period of time after they were diagnosed with or treated for a disease. The overall survival rate is often stated as a 5-year survival rate, which is the percentage of people in a study or treatment group who are alive 5 years after diagnosis or treatment.
Progression-free survival (PFS)	The length of time during and after treatment in which a patient is living with a disease that does not get worse.
Tumor response rate	
• Complete response (CR) rate	• The disappearance of all signs of cancer in response to treatment. This does not always mean the cancer has been cured. Also called complete remission.
• Partial response (PR) rate	• A decrease in the size of a tumor, or in the extent of cancer in the body, in response to treatment. Typically defined as a 50% reduction in tumor burden. Also called partial remission.
Time to progression (TTP)	A measure of time after a disease is diagnosed (or treated) until the disease starts to get worse.
Disease-free survival (DFS)	The length of time after treatment for a specific disease during which a patient survives with no sign of the disease. Disease-free survival may be used in a clinical study or trial to help measure how well a new treatment works. Also called disease-free progression (DFP).

Note. Definitions obtained from National Cancer Institute website (NCI, 2010).

and it is sensitive to cytostatic as well as cytotoxic mechanisms of interventions (unlike overall response rate). Unlike TTP, it incorporates the clinically relevant event of death, which increases sensitivity to important harmful mechanisms and avoids substantial bias that arises when deaths are censored by measures such as TTP (Fleming, et al., 2009). Therefore, the use of PFS as an endpoint is increasingly seen in oncology research.

DISCLOSURES

The author has no potential conflicts of interest to disclose.

REFERENCES

Burzykowski, T., Buyse, M., Yothers, G., Sakamoto, J., & Sargent, D. (2008a). Exploring and validating surrogate endpoints in colorectal cancer. *Lifetime Data Analysis 14*(1), 54–64.

Burzykowski, T., Buyse, M., Piccart-Gebhart, M. J., Sledge, G., Carmichael, J., Luck, H. J.,...Therasse, P. (2008b). Evaluation of tumor response, disease control, progression-free survival, and time to progression as potential surrogate end points in metastatic breast cancer. *Journal of Clinical Oncology, 26*(12), 1987–1992. doi:10.1200/JCO.2007.10.8407

Buyse, M., Burzykowski, T., Carroll, K., Michiels, S., Sargent, D. J., Miller, L. L.,...Piedbois, P. (2007). Progression-free survival is a surrogate for survival in advanced colorectal cancer. *Journal of Clinical Oncology 25*(33), 5218–5224. doi:10.1200/JCO.2007.11.8836

Fleming, T. R. (2005). Surrogate endpoints and FDA's accelerated approval process. *Health Affairs (Millwood), 24*(1), 67–78. doi:10.1377/hlthaff.24.1.67

Fleming, T. R. (2006). Standard versus adaptive monitoring procedures: A commentary. *Statistics in Medicine, 25*(19), 3305–3312; discussion 3313–3304, 3326–3347. doi:10.1002/sim.2641

Fleming, T. R., & DeMets, D. L. (1996). Surrogate end points in clinical trials: Are we being misled? *Annals of Internal Medicine, 125*(7), 605–613.

Fleming, T. R., Rothmann, M. D., & Lu, H. L. (2009). Issues in using progression-free survival when evaluating oncology products. *Journal of Clinical Oncology, 27*(17), 2874–2880. doi:10.1200/JCO.2008.20.4107

Hackshaw, A., Knight, A., Barrett-Lee, P., & Leonard, R. (2005). Surrogate markers and survival in women receiving first-line combination anthracycline chemotherapy for advanced breast cancer. *British Journal of Cancer, 93*(11), 1215–1221.doi:10.1038/sj.bjc.6602858

Hughes, M. D. (2008). Practical issues arising in an exploratory analysis evaluating progression-free survival as a surrogate endpoint for overall survival in advanced colorectal cancer. *Statistical Methods in Medical Research, 17*(5), 487–495. doi:10.1177/0962280207081860

Miksad, R. A., Zietemann, V., Gothe, R., Schwarzer, R., Conrads-Frank, A., Schnell-Inderst, P.,...Siebert, U. (2008). Progression-free survival as a surrogate endpoint in advanced breast cancer. *International Journal of Technology Assessment in Health Care, 24*(4), 371–383. doi:10.1017/S0266462308080495

National Cancer Institute (NCI). (2009). Dictionary. Retrieved from www.cancer.gov/dictionary

Sargent, D. J., Patiyil, S., Yothers, G., Haller, D. G., Gray, R., Benedetti, J.,...de Gramont, A. (2007). End points for colon cancer adjuvant trials: Observations and recommendations based on individual patient data from 20,898 patients enrolled onto 18 randomized trials from the ACCENT Group. *Journal of Clinical Oncology, 25*(29), 4569–4574. doi:10.1200/JCO.2006.10.4323

Sargent, D. J., Wieand, H. S., Haller, D. G., Gray, R., Benedetti, J. K., Buyse, M.,...de Gramont, A. (2005). Disease-free survival versus overall survival as a primary end point for adjuvant colon cancer studies: Individual patient data from 20,898 patients on 18 randomized trials. *Journal of Clinical Oncology, 23*(34), 8664–8670. doi:10.1200.JCO.2005.01.6071

Schatzkin, A. (2000). Intermediate markers as surrogate endpoints in cancer research. *Hematology/Oncology Clinics of North America, 14*(4), 887–905.

Shi, Q., & Sargent, D. J. (2009). Meta-analysis for the evaluation of surrogate endpoints in cancer clinical trials. *International Journal of Clinical Oncology, 14*(2), 102–111. doi:10.1007/s10147-009-0885-4

Tang, P. A., Bentzen, S. M., Chen, E. X., & Siu, L. L. (2007). Surrogate end points for median overall survival in metastatic colorectal cancer: Literature-based analysis from 39 randomized controlled trials of first-line chemotherapy. *Journal of Clinical Oncology, 25*(29), 4562–4568. doi:10.1200/JCO.2006.08.1935