Editorial

Primary endpoints in cancer trials

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There is an ongoing discussion about the selection of the most appropriate primary endpoint in cancer trials. Most papers are comparing progression-free survival (PFS) with overall survival (OS). Alternatives could be disease-free survival (DFS) or time to treatment failure (TTF). Another option could be the quality of life.

For the patient the OS is of greater importance than PFS. On the other hand the use of PFS gives a faster answer whether there is a difference between two treatments and it might be cheaper as well (1). If there is a high correlation between both endpoints, PFS can be used as primary endpoint. Otherwise there might be a difference in PFS between the treatment groups but not for OS. Fleming et al. are presenting some examples (2).

Usually the hazard ratios for OS are closer to 1 compared with those for PFS.

If one is interested in testing the hypothesis whether there is a difference between two treatments, PFS is the appropriate endpoint. In a randomised trial the treatment groups (for simplicity two groups are assumed) are comparable with all factors except the therapy. After a progression this situation changes dramatically. Some of the patients with a progression will receive a second line therapy. From this time on the study turns from a randomised trail into an observational study.

If OS is the primary endpoint the question which can be addressed with this design is whether the beginning with one or the other treatment has an effect on OS.

Broglio and Berry (3) are describing the idea of partitioning the survival time (OS) into two parts as the sum of PFS and the survival time past progression (SPP): OS = PFS + (OS-PFS) = PFS + SPP.

If the time SPP is getting longer compared to PFS, the correlation between PFS and OS is getting smaller and PFS is not a good surrogate for OS.

In this issue of the Journal of Thoracic Disease, Zietemann et al (4) are presenting data showing very precisely this problem. Patients with NSCLC were splitted into two groups. The responders with any response to first line therapy or at least with stable disease form one group, denoted with DC (= disease control). The patients with progression or not evaluable form the other group. Patients in the later group did receive less frequent second line therapy (47%) compared to patients with DC (60%) but if so much earlier.

There is no proper statistical approach to account for these decisions. The authors are discussing the pitfalls in using a time-dependent confounder, the change into a progression.

Their message is that in some of the recent lung cancer trails the subsequent therapies were not taken into account. There are some proposals but also problems with adequate analysis.

No potential conflict of interest.

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The use of a progression as definition of a response and the subsequent analysis of the OS depending on the response status again can lead to highly biased results (5). The idea is to apply a landmark model using the response at a certain time.

Following the proposal of Broglio and Berry in splitting the survival time (OS) into two parts, prior and post progression (OS = PFS + SPP) the problem gets clear.

Assume the median PFS time under treatment A is 15 months and under treatment B 10 months. Under certain assumptions the hazard ratio will be around 1.5 (=15/10). If the median SPP in both treatment groups is about 10 months the HR drops down to 1.25 (= 25/20).

If the progression rate is high and the number of deaths do not exceed the number of patients with progression the study not showing a difference in OS might be underpowered. The variances of the harzard ratio for OS and for PFS will be similar, but hazard ration for OS is closer to 1.0.

There is no optimal solution available and the ability to demonstrate an advantage in OS will be very difficult due to the crossover at the time of progression. The same problem is present in identifying predictive markers. Should these markers be selected with respect to PFS or to OS (6)?

There is no adequate solution available and the discussion about the selection of the proper primary endpoint will continue.

The proposal of Zietemann et al (4) to predefine the second line and further treatments at study entry will certainly be very helpful in standardizing the therapy and also for the statistical analysis.

References

1. Pollock BH. Cheaper, faster, better: chasing the elusive clinical trial end point. J Clin Oncol 2009;27:2747-8.
2. Fleming TR, Rothmann MD, Lu HL. Issues in using progression-free survival when evaluating oncology products. J Clin Oncol 2009;27:2874-80.
3. Broglio KR, Berry DA. Detecting an overall survival benefit that is derived from progression-free survival. J Natl Cancer Inst 2009;101:1642-9.
4. Zietemann VD, Schuster T, Duell THG. Post-study therapy as a souce of confounding in survival analysis of first line studies in patients with advanced non small cell lung cancer. J Thorac Dis 2011;3:88-98.
5. Anderson JR, Cain KC, Gelber RD. Analysis of survival by tumor response and other comparisons of time-to-event by outcome variables. J Clin Oncol 2008;26:3913-5.
6. Shepherd, FA; Tsao, MS. Epidermal growth factor receptor biomarkers in non-small-cell lung cancer: a riddle, wrapped in a mystery, inside an enigma. J Clin Oncol 2010;28:903-5.

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