CASE STUDY

BY MAURIE MARKMAN

What Must Research Subjects Be Told Regarding the Results of Completed Randomized Trials?

Federal research regulations require investigators to inform research subjects of "significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation."[1] However, the determination of what is, and what is not, relevant to disclose is open to interpretation and potential ethical conflict. The recently reported results of a multi-center randomized Phase III trial (in which the author of this commentary was the principal investigator) examining "maintenance/consolidation therapy" of advanced ovarian cancer provide a poignant example of the complexity of this fundamental issue.[2]

Randomized Phase III Trial of "Maintenance/Consolidation" Therapy

Standard treatment of advanced ovarian cancer includes the administration of 6 cycles of two classes of highly active cytotoxic anti-neoplastic agents (platinum/taxane).[3] Despite the very high objective response rate (60-90%) achieved with this therapy, disease recurrence is the rule, rather than the exception, and the large majority of individuals with the malignancy ultimately die as a direct result of complications of progressive cancer.[4]

In an effort to improve upon this anticipated outcome, investigators in two large National Cancer Institute-sponsored cooperative groups (Southwest Oncology Group, Gynecologic Oncology Group) initiated a Phase III randomized trial examining the continuation of paclitaxel (one of the drugs employed in the initial treatment regimen)[5] in women with advanced ovarian cancer who had achieved a complete response (e.g., no symptoms of cancer, no evidence of disease on physical examination, normal laboratory and radiographic evaluation) following 5-6 cycles of primary chemotherapy.[6] Patients treated in this trial received therapy with single agent paclitaxel once a month (every 28 days) for either 3 monthly cycles or 12 monthly cycles.

The study was designed to enroll 450 research subjects; its primary endpoints were *progression-free survival* (PFS; time from study entry until the development of evidence of progressive disease) and *overall survival*. A prospectively planned interim analysis performed when 50% of the research subjects had entered the trial revealed a highly statistically significant improvement in PFS in favor of the 12-cycle treatment arm (median 3-cycle PFS: 21 months; median 12-cycle PFS: 28 months; p = 0.0023; HR= 2.31). Based on the substantial differences in PFS, the Southwest Oncology Group Data Safety and Monitoring Committee (DSMC) elected to close the trial at this point, and inform all study participants of the results.[7] Of note, at the time of discontinuation of this study there were no differences in overall survival between the study arms, although a total of only 17 deaths were recorded in the entire patient population.

Implications of Study Results for Standard Clinical Practice

Several points should be made in discussing the interpretation of the results of this somewhat controversial study. First, there were no major imbalances in prognostic factors between the two study arms, or concerns with the statistical design of the trial. As a result, it would be inappropriate to suggest the outcome was due to either of these factors. Second, even if an overall survival benefit would have been observed if the study had been continued to meet its initial planned accrual goal, such an outcome is now highly unlikely as it can be anticipated that research subjects randomized to the 3-cycle arm, when informed of the results of the study, would have elected to receive additional treatment prior to developing disease progression.

Thus, the question of whether 12 additional months of single agent paclitaxel favorably affects overall survival, or only PFS, will almost certainly remain unan-

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swered (unless some other group of investigators elects to address this issue in another randomized trial). As a result, in the absence of data documenting a favorable impact on overall survival, it would be inappropriate to definitively conclude that this management strategy should be considered the standard of care. Conversely, based on existing information, it would be equally incorrect to state that we currently know this therapeutic strategy will not influence ultimate survival in advanced ovarian cancer. The controversy surrounding this trial centers on how we should interpret the results of the study in the absence of a definitive answer to the question of the impact of this novel management approach on overall survival in the malignancy.

However, respect for patient autonomy leads to the logical conclusion that it is the individual patient who must ultimately decide the clinical value of additional paclitaxel chemotherapy, how much weight she will give to the now documented statistically significant improvement in PFS, and its impact on both delaying symptoms of the disease and knowledge that the cancer has recurred. The demonstrated benefits (improvement in PFS) and potential benefits (improvement in overall survival) associated with continuation of paclitaxel for up to an additional year must be balanced against the possible toxicity of therapy. This toxicity includes both physical (increasing fatigue, numbness and tingling of the hands and feet) and psychological/emotional (including persistent hair loss until treatment is stopped) effects of the chemotherapy. It is the responsibility of the treating physician to fully discuss the implications of the study findings with a woman who is a potential candidate for this management strategy (i.e., complete response to primary chemotherapy and absence of evidence of serious neurological symptoms) and permit the patient to decide what course of action is most appropriate for her.

Does a physician-investigator's decision not to inform his/her patient of these trial results constitute medical paternalism? Is it appropriate for a physician to unilaterally make such a management decision for a patient with advanced ovarian cancer?

Implications of Study Results for Future Clinical Trials

It is perhaps the impact of this trial on the conduct of ongoing and future clinical investigative efforts in ovarian cancer that raises the greatest concern for ethical conflict. The issues are as follows:

- Do the results of this trial, which satisfied prospectively defined criteria for early closure based on a major improvement in progression-free survival, mandate that all research subjects being treated in ongoing, or future, primary chemotherapy trials in ovarian cancer be informed of this outcome?

- If a physician-investigator answers no, because at present it is unknown if this strategy will result in a statistically significant improvement in overall survival, what does such a conclusion say about the physician-investigator's attitude regarding patient autonomy? Should it be up to the patient to decide if a substantial prolongation (as revealed in this randomized trial) of the time to documented disease recurrence (delay in development of symptoms and knowledge the primary therapy did not cure the cancer) justifies the potential side effects of therapy (e.g., continued hair loss, peripheral neuropathy)? Does a physician-investigator's decision not to inform his/her patient of these trial results constitute medical paternalism? Is it appropriate for a physician to unilaterally make such a management decision for a patient with advanced ovarian cancer?

- If a physician-investigator elects not to inform a patient regarding the results of the maintenance/consolidation therapy trial, but instead enters her into a primary chemotherapy study which does not permit maintenance therapy (e.g., treatment discontinued following 6 chemotherapy cycles), would it be unreasonable to claim that the investigator has a conflict of interest? What if a physician-investigator stood to benefit directly (e.g., academic or financial reward) from entering the patient into the trial that involved no-maintenance-therapy?

- Who should decide what to tell potential and current research subjects about randomized trial results, and what should be the criteria for making that decision? For example, the Food and Drug Administration (FDA) frequently requires overall survival to be the endpoint in registration studies of new cytotoxic agents employed in cancer management.[8] A

pharmaceutical company seeking FDA approval of a novel anti-cancer drug in ovarian cancer may be required to have all patients discontinue therapy following the initial treatment program (perhaps because the maintenance approach is not FDA approved) and then be observed until progression, with the primary study endpoint being overall survival. Although the importance of an improvement in overall survival as a clinical and research goal is obvious, this may not be the only endpoint relevant to a patient.

• Is it critical to inquire if there are alternative study designs that would permit a maintenance therapy approach, but at the same time allow for the necessary evaluation of new drugs in this difficult disease? For example, if an identical paclitaxel maintenance program were delivered in both arms of a randomized trial (control and experimental), then a demonstrated improvement in overall survival (or PFS) associated with the experimental regimen would be appropriately considered to be due to the anti-neoplastic activity of the new agent. While this study design would allow patient-subjects to receive maintenance therapy, the trial will still permit a valid test of a novel anti-cancer drug.

• Finally, what is the role of the Institutional Review Board (IRB) in this debate? Considering the extreme importance of patient autonomy, should IRBs require that all future informed consent documents describing studies of primary chemotherapy of advanced ovarian cancer specifically mention the option of maintenance/consolidation therapy, based on the results of the published randomized trial, even if the principal investigator, pharmaceutical sponsor, or FDA, do not support this requirement? Who should decide what information to give to current and future research subjects?

There are no simple answers to the questions posed above. As this case study has shown, the boundary between patient autonomy and medical paternalism is often not clear. IRBs and others concerned with the complex process of informed consent must enter into a discussion about whether investigators should provide inconclusive or conflicting information to potential and current research subjects. Of particular importance is whether this information should be provided to individuals with serious medical illness whose vulnerability may make it difficult for them to understand and deal with either inadequate or excessive data.

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References

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