As recruitment for oncology clinical trials has become more difficult, there appears to have been an increase in the number of studies that allow patients in the control arm to “crossover” and receive the experimental therapy after disease progression. Although some researchers worry that allowing such crossover may abolish gains in progression-free survival in the experimental arm, the possibility that crossover might inadvertently benefit the experimental arm has not been addressed. In clinical trials in which the experimental agent has little or no intrinsic activity and is used to modulate an active combination, such crossover might negatively affect the overall survival of the control arm. Because resistance to the active combination—manifested as disease progression—has occurred, the likelihood of benefit from adding the experimental drug is reduced. Consequently, patients who were randomly assigned to the control arm continue to receive the now inactive combination after crossover, whereas patients in the experimental arm who discontinue study participation may seek out potentially effective salvage regimens. This difference in subsequent therapies may confer an advantage to the experimental arm that is manifested as gains beyond those achieved in progression-free survival, gains that occur not because the experimental therapy induced a change in tumor biology that persists beyond treatment discontinuation but because the control arm suffers by continuing to receive a therapy on which their tumor is progressing. Such an outcome may explain the recently reported trial results for iniparib in triple-negative breast cancer. Given that allowing patients in the control arm to receive the experimental agent may confound interpretation of overall survival, such crossover should not be used indiscriminately, especially if the experimental agent has little or no intrinsic activity.

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Investigators who conduct clinical trials in oncology are finding recruitment increasingly difficult. The number of patients who volunteer for clinical trials in the Western world continues to decline, and many patients considering participation in clinical trials find the possibility of being randomly assigned to a placebo or a control drug unattractive, especially if the experimental drug is perceived as being very promising (1–5). To deal with this latter problem, clinical trials sometimes offer patients who are randomly assigned to the control arm the option of receiving the experimental agent at the time of disease progression.

The consequences of allowing crossover may vary with the agent being tested. For an agent such as a poly(ADP-ribose) polymerase (PARP) inhibitor, which is encumbered by high expectations, especially in a disease as aggressive as triple-negative breast cancer, one can understand why an attractive strategy to augment recruitment would be to allow patients who were initially randomly assigned to the control arm the opportunity to receive the experimental drug after documented disease progression. Such “crossover” is typically allowed for patient benefit and not for formally comparing the outcome of interest. Unfortunately, however, this strategy may not always be innocuous and, as discussed below in the case of the recently reported iniparib trial, may affect the outcome (6). The effect of crossover on the subsequent clinical course after disease progression depends on several factors, particularly the mechanism of action and the intrinsic activity of the experimental drug. For example, a renal cell carcinoma patient whose disease has progressed on interferon alfa (IFN-α) might be expected to benefit from the administration of sunitinib, a drug whose mechanism of action, albeit still incompletely understood, likely has nothing in common with IFN-α. Such was the outcome in the clinical trial that compared sunitinib vs IFN-α in metastatic renal cell carcinoma, in which almost 60% of the patients who were randomly assigned to IFN-α were eventually treated with sunitinib or another vascular endothelial growth factor receptor (VEGFR) inhibitor (7,8). The resulting posttrial survival was nearly 3 months (ie, 10.4 weeks) longer for patients who were randomly assigned to IFN-α compared with those randomly assigned to sunitinib, a result most likely due to a benefit from the VEGFR inhibitor (7–9). In the case of iniparib or, for that matter, PARP inhibitors, this paradigm may not apply. PARP inhibitors generally lack intrinsic activity against solid tumors that do not harbor BRCA1 and BRCA2 mutations or possess a “BRCA-like” phenotype; in the case of triple-negative breast cancer, one can argue that the value of PARP inhibitors resides not in their intrinsic activity butprimarily in their use as modulators of drug activity (eg, in the case of the iniparib trial, they were used to modulate...
the activity of the gemcitabine plus carboplatin “backbone”). In cases where the experimental agent lacks intrinsic activity, its success depends on its ability to modulate the activity of the backbone drug combination (gemcitabine and carboplatin), and one cannot expect that modulation will be as effective in a patient whose tumor has progressed while the patient has been receiving gemcitabine and carboplatin as in a patient whose tumor is exposed to these agents for the first time. Indeed, this was the observation in the iniparib trial: Among 30 patients randomly assigned to the control arm who crossed over to receive iniparib with gemcitabine and carboplatin, only one unconfirmed response was observed (an objective response rate of 3%), a dramatic difference compared with the 52% overall response rate in the patients who were initially randomly assigned to iniparib in combination with gemcitabine and carboplatin (6). Given the median progression-free survival of only 3.6 months in the control arm, the tumors in the patients who crossed over were for the most part rapidly growing and clearly refractory to the backbone drug combination. Thus, the outcome following crossover—patients who crossed over received a median of 1.5 cycles of iniparib, 83% discontinued treatment after one or two cycles, and in only one (3%) was an unconfirmed partial response recorded—is not surprising. We note that although the published data on iniparib are sparse, Clarke et al. (10) showed that sensitization to temozolomide by the PARP inhibitor, ABT-888, was lost with the development of temozolomide resistance in glioblastoma xenograft cell lines. This finding underscores the clinical observation with iniparib that sensitization of de novo resistance cannot be expected to translate into sensitization of acquired tolerance.

An ineffective crossover (ie, one that confers no benefit to the patient) can have consequences that confound the interpretation of the trial results. For example, in the iniparib trial, more than half of the patients who were randomly assigned to the control arm ultimately crossed over and received the experimental combination after disease progression and had no benefit. These patients, who received a median of 1.5 cycles of chemotherapy after crossover, continued to receive a therapy to which their tumors were tolerant for one to several months rather than ending study participation and receiving alternate therapies (albeit of limited efficacy) that potentially had a greater likelihood of success compared with the experimental combination. Given that most cancer patients in many developed countries including the United States receive chemotherapy even in their last month of life (11), it seems safe to assume that the patients who were initially randomly assigned to iniparib and experienced disease progression would have gone on to receive alternate therapies. Thus, in clinical trials of iniparib or any agent that is used as a modulator, allowing crossover risks encumbering the control arm with the continuation of an ineffective therapy. This in turn may compromise the overall survival of the patients who crossed over, giving the experimental arm an unfair advantage. In addition, it would not be surprising in the iniparib trial or a similar trial to find that the patients with better performance status were the ones who crossed over, further compromising the control arm by withholding or delaying alternate therapies in patients who were most likely to benefit. For example, in metastatic non–small cell lung cancer, a disease that, like metastatic triple-negative breast cancer, has an overall survival of about 1 year, rapid progression, declining performance status, and increased symptom burden make these patients poor candidates for further treatments, and none is usually administered (12). In the triple-negative breast cancer patients, a similar prejudice could have resulted in the continuation of the ineffective backbone primarily in those with better performance status. Evidence that the patients in the control arm of the iniparib trial received ineffective treatment after crossover is suggested not only by their 3% objective response rate but also by the differences in overall survival between the control and experimental arms. We have previously shown that the magnitude of the difference in progression-free survival between the control and experimental arms of a trial is usually similar to the magnitude of the difference in overall survival (13). This similarity in progression-free survival and overall survival differences occurs because current therapies do not change the underlying biology of the tumors but instead have effects only while they are being administered (13). In the iniparib trial, however, the difference in overall survival (4.6 months) was twice the difference in progression-free survival (2.3 months). Why would this occur? The authors noted that a slight imbalance in prognostic factors that favored the iniparib group could have translated into a more favorable (ie, slower growing) tumor biology, leading to a difference in progression-free survival and then a larger difference in overall survival (6). However, we posit an alternate explanation: The cohort that was initially randomly assigned to iniparib appeared to gain because the control arm suffered. With more than half of the patients randomly assigned to the control arm receiving a therapy to which their tumors were refractory as their first regimen after progression, the group initially randomly assigned to iniparib had an advantage in that their post-progression therapies may have resulted in differences in posttrial survival, to the detriment of the control group. In addition, the impact of allowing crossover might be expected to be greater in patients with more advanced disease because their shorter overall survival means a greater and likely more substantial part of their remaining time is spent receiving an ineffective therapy. A preliminary report of the recently completed randomized phase III study appears to support this notion (14).

There are other concerns about allowing crossover beyond those described above. Trials that use modulators of drug activity must pay close attention to the doses of the drugs that comprise the backbone (in the case of the iniparib trial, gemcitabine and carboplatin). Because survival differences might be lessened at higher backbone doses, lower (suboptimal) doses of the backbone might result in an apparent benefit for the modulator in a randomized trial. Whether this happened in the iniparib trial cannot be ascertained but seems less likely given that the response rate in the control arm was 32%, which suggests that the doses of gemcitabine and carboplatin were adequate. However, for both cisplatin and carboplatin, there are substantial data, primarily in ovarian carcinoma, indicating a steep dose–response curve, including 1) preclinical studies (15), 2) a retrospective meta-analysis (16), and 3) reports of responses in patients with tumors refractory to standard doses when higher doses were administered (17,18). Similar data exist for other chemotherapeutic agents. Therefore, investigators must be careful when designing a clinical trial to avoid reducing doses of the backbone drugs in both the control and the experimental arms of a study.
Finally, beyond PARP inhibitors in triple-negative breast cancer, where else might post-progression crossover confound outcomes? This may occur to some extent in patients whose tumors harbor BRCA1 and/or BRCA2 mutations where, in addition to its intrinsic antitumor activity, PARP inhibitors may be used with chemotherapy backbones to modulate the activity of the backbone. However, in general, one must be most concerned in cases where the experimental drug has very little or no intrinsic activity and is being used primarily to modulate the efficacy of an active backbone. For example, as data continues to emerge suggesting that alternative pathways might be recruited as a mechanism of resistance by tumor cells, novel combinations of targeted therapies are being proposed. One example is the use of a mitogen-activated protein/extracellular signal-regulated kinase kinase (MEK) inhibitor in combination with an inhibitor of the epidermal growth factor receptor, the insulinlike growth factor receptor, or the mammalian target of rapamycin (19). Because MEK inhibitors to date have failed to demonstrate much clinical antitumor activity as single agents, their use in combination regimens will be primarily to prevent the recruitment of the RAS/MEK/ERK pathway as a mechanism of drug resistance (20–24). Whereas a MEK inhibitor may assist a second agent in first-line therapy (as might a PARP inhibitor in triple-negative breast cancer), its ability to do so may be reduced once resistance has developed, such that crossover will be ineffective and possibly compromise the overall survival of a control arm. We also note that many have raised the possibility that post-progression crossover designs where an effective agent is administered may abolish gains in progression-free survival when overall survival is assessed. This scenario, unlike the one discussed for the iniparib trial, would involve an agent that has intrinsic activity.

In summary, although allowing cancer patients who enroll on a clinical trial the option to receive the experimental agent after disease progression might be more appealing to patients, referring physicians, and clinical investigators and thus help enhance accrual, this strategy should not always be used. For agents with little or no intrinsic activity, where the goal is to enhance the activity of a previously established regimen, such a design might inadvertently favor the experimental arm, invalidating overall survival analyses.

References

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