Treatment Beyond Progression: Is It Moving from Belief to Evidence?

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One of the first lessons taught to budding oncologists is the rule that treatments should be initiated with a clear goal in mind and that therapy should be revised or reconsidered if that objective is not achieved. This is particularly true in the treatment of metastatic disease because a therapy is usually initiated to relieve symptoms and prolong good quality life, and if symptoms are not improved, continuing futile treatment is not in the best interests of the patient. In the clinical trial arena, disease is assessed every two to three cycles and treatment is quickly considered unsuccessful if there is tumor growth.

Recently, however, there has been a move to reconsider this treatment paradigm for agents that may have a different mode of activity. There is discussion about continuation of antiangiogenic agents in renal cell carcinomas and possibly other tumor types. And there has been an ongoing discussion regarding the role of treatment beyond progression with anti-human epidermal growth factor receptor (HER)-2 agents in metastatic breast cancer. In this issue of *The Oncologist*, a manuscript by Extra and colleagues describes the Hermine trial, a large French study that addresses this issue [1].

The Hermine trial was an observation trial that reviewed 623 patients who were treated according to the oncologists' normal clinical practice of either continuing the treatment

beyond progression or stopping it as is usual with cytotoxic therapy. The endpoints of the trial included the duration of treatment, efficacy, and cardiac safety. A subanalysis was done to compare the overall survival (OS) times of the patients who received the drug as first-line therapy. The authors report on the median time to progression in the first-, second-, and third-line groups, and in particular emphasize that the OS time and time to disease progression were significantly longer in those who continued receiving trastuzumab than in those who discontinued at progression, with a >27.8-month OS time, compared with a 16.8-month OS time. No excess cardiac toxicity was observed, implying that continued treatment is safe. The limitation of this study is that it was observational and not randomized and that the groups are not completely comparable. The strength of the study is that it reflects normal practice.

This study adds to the accumulating evidence that there may be benefit in continuing trastuzumab past progression. Many investigators have cited early preclinical work showing a rebound growth effect when anti-HER-2 therapy is discontinued, but in vitro growth cannot be used as strong evidence for a similar effect in patients [2]. However, there have been a number of clinical reports over the last decade, many much smaller than the Hermine trial, that support the results of the current French study [3–10]. These retrospec-

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tive studies have been criticized because there is no way to determine whether the patients who continued the drug had other reasons for the superior outcomes. In the Hermine study, there were imbalances that were clearly discussed by the authors. The patients who continued were noted to have a better prognosis at treatment initiation with a lower grade, longer disease-free interval, fewer visceral metastases, and more adjuvant hormone therapy. A criticism is that these differences detract from using retrospective studies as evidence. A counter may be that these factors may be used in the clinic to select who may benefit from continued treatment.

As well, recently randomized trials have added further and more robust evidence for continued therapy. The German trial, German Breast Group 26, reported by Von Minckwitz et al. [11], randomized patients who were progressing on a taxane and trastuzumab to capecitabine with or without continued trastuzumab and showed a longer progression-free survival interval for the combined arm. That trial had difficulties enrolling, did not reach its target accrual, and has been criticized for this lower power, but it has still shown a benefit in terms of its primary endpoint. The theory purported for the effect is that trastuzumab may be acting as a chemotherapy sensitizer, and when a new cytotoxic is added, it provides further benefit over chemotherapy alone. A similar trial was initiated in the U.S. with vinorelbine instead of capecitabine, but it also closed early. A study of capecitabine with or without lapatinib for patients progressing after prior anthracyclines, taxanes, and trastuzumab also lends support to the strategy of continued anti-HER-2 suppression, albeit with a different agent [12].

If adding a cytotoxic is effective, the obvious question is whether adding another HER-2 agent to trastuzumab would have a similar and possibly less toxic effect. A study reported this year by Blackwell et al. [13] randomized patients progressing on trastuzumab to either single-agent lapatinib or continued trastuzumab with lapatinib. That trial initially reported a longer progression-free survival time, but more recently it showed a longer OS time with the dual blockade of two anti-HER-2 agents, providing further support for treatment beyond progression with trastuzumab. The effect was seen despite the fact that the patient population was a more heavily pretreated population than in the Von Minckwitz et al. [11] study and many of the retrospective reports.

Does this suggest that we should change our treatment paradigms in HER-2⁺ disease? Many new agents are now being tested and it cannot be assumed that continued treatment with newer agents will be both effective and safe. With adjuvant HER-2 treatments, the number of persons with metastatic disease is decreasing in this subtype of breast cancer. This will challenge the medical community to do proper clinical trials on all new agents and on all the questions that need to be answered to understand the optimal treatment strategies.

What is clear from both the randomized trials and observational studies is that, for patients with breast cancers that overexpress HER-2, the most effective treatment is HER-2 blockade and continuation of some form of therapy that addresses this factor is important. Treatment guidelines that limit access to anti-HER-2 therapies to one or two lines of treatment are not accounting for the molecular makeup of the cancer and the overwhelming effect of HER-2. Studies such as the Hermine study are important in highlighting this effect in a general population of “real life” breast cancer patients as well as in the rarified group who enter clinical trials. Although there are economic considerations for continued HER-2 treatment in many jurisdictions, the comparison of effective therapy that prolongs good quality survival with significantly less active treatment should favor anti-HER-2 treatment in a proper pharmacoeconomic assessment. Again, as oncologists we must consider the performance status of the patient and the goals of the therapy to best address the continuation of any treatment and understand that one size or treatment strategy may not fit all patients.

What was in the realm of belief and dogma is moving closer to an evidence-based treatment strategy. We may never have large randomized trials confirming the role of treatment beyond progression in HER-2–overexpressing breast cancer, but there is accumulating evidence of benefit in good performance status patients.

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