Commentary

Addressing Overtreatment in Breast Cancer

The Doctors' Dilemma

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Concerns about the potential harm of treatments for cancer have grown because population-based screening has markedly increased the number of patients with relatively favorable prognosis.[1-6] Approximately half the 280,000 patients diagnosed with breast cancer this year will have relatively favorable prognosis: one-quarter will be diagnosed with ductal carcinoma in situ and another quarter will be diagnosed with invasive disease with relatively favorable prognosis (estrogen receptor [ER]-positive, human epidermal growth factor receptor 2 [HER2]-negative, node-negative, tumor size < 2 cm). Although guidelines clearly show benefit of locoregional and systemic treatments in different subgroups,[7-9] patients with favorable prognosis are vulnerable to overtreatment because the absolute net benefit of different treatments may be small and difficult to quantify in individual cases. Thus, clinicians face the prospect of doing more harm than good if the treatment plan is too aggressive or potentially lifesaving therapy is omitted. Advances in personalized treatment hold the promise of increasing the certainty of the treatment benefit of different treatments in individual patients, but insufficient attention has been paid to the challenges to treatment decision-making.[10]

ADDRESSING THE CHALLENGES IN TREATMENT DECISION-MAKING

Cancer treatment decision-making is challenging because there are multiple effective therapies that are interconnected, and there is a complex interplay between their benefits and risks. Furthermore, treatment recommendations are based on increasingly complicated clinical information related to extent of disease, tumor biology, and host factors that is revealed variably over time after initial diagnosis. Integrating this information into a treatment plan is challenging because different specialists direct the various treatments. In this context, clinicians need to address 3 key challenges in decision-making.

Address the Interplay Between Benefits and Risks of the Treatment Options

The absolute net benefit in disease-free survival of a given treatment option is generally diminished by the other treatment options that are incorporated into the management plan, whereas the burden and morbidity of the treatment options are cumulative. For example, the addition of chemotherapy[11] or endocrine therapy to surgery and radiotherapy (RT)[12] not only reduces distant recurrence, it halves locoregional recurrence, which has implications for surgical management. This interplay is particularly important for patients with favorable prognosis because the tipping point of doing more harm than good may be quite low. This principle of diminishing returns of treatment benefits against cumulative harms has motivated initiatives to reduce morbidity and burden of locoregional therapies. For example, sentinel node biopsy has increasingly replaced complete axillary dissection in patients with limited nodal metastases who undergo breast-conserving surgery with RT and systemic therapy, because the procedure is less morbid, has high clinical utility, and confers equivalent survival benefit. The marked decline of mastectomy underscores the powerful influence of a definitive evidence base, demonstrating that in most patients the 2 approaches confer the same survival benefit with negligible differences in local recurrence.[13] However, the increasing use of contralateral prophylactic mastectomy underscores the need to address the interplay between benefits and risks of treatment. Contralateral prophylactic mastectomy is currently performed on 15% to 20% of patients who receive mastectomy. Yet, the use of systemic therapy reduces the risk of

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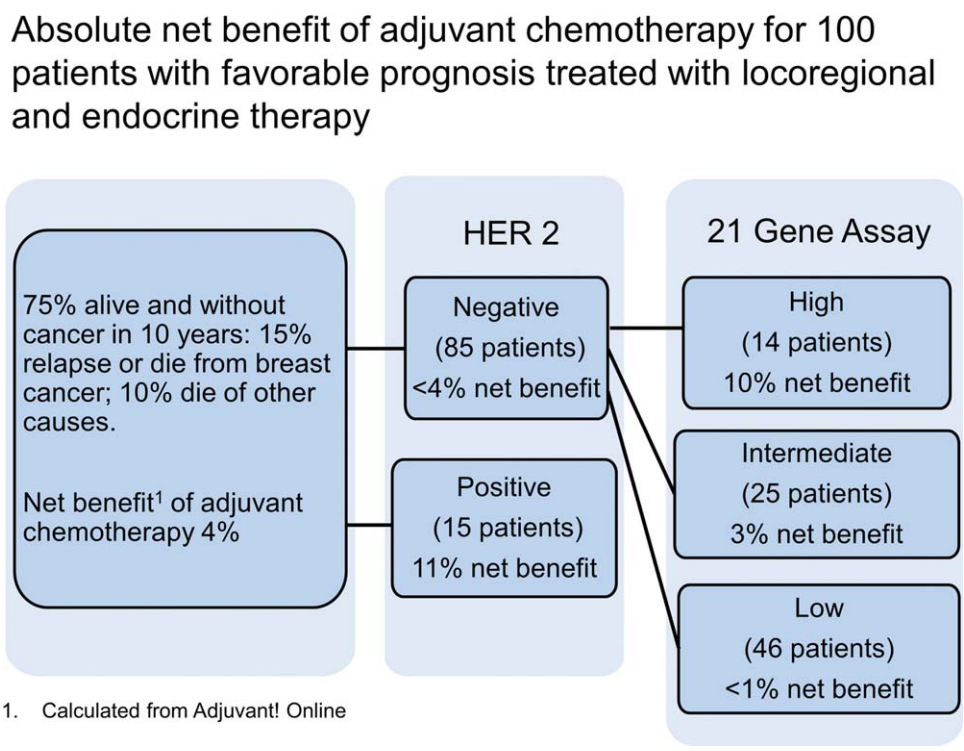

Figure 1. Chart shows absolute net benefit of 10-year disease-free survival of chemotherapy in patients treated with locoregional and endocrine therapies. The patient with favorable prognosis is a 60-year-old female with average health for age, with an estrogen receptor (ER)-positive, average grade tumor less than 2 cm with negative pathologic lymph nodes.

contralateral cancer to such a low level that most patients (with the exception of BRCA mutation carriers) have virtually no possibility of benefiting from contralateral surgery with regard to disease-free survival.[14]

Clarify the Level of Certainty of the Treatment Effect

Perhaps more challenging for clinicians is the need to clarify the level of certainty of the treatment effect for an individual patient. The level of certainty is determined by: 1) the strength of the evidence for a given treatment option in a particular clinical subgroup and 2) the accuracy of an evaluative testing strategy that places a patient in a particular subgroup. The level of certainty required to omit therapy (or to choose a less aggressive treatment option) is greater than that required to commit to more aggressive treatment plan. Support for less aggressive treatment for cancer requires identifying patient subgroups for which the treatment is nearly futile or at equipoise. This higher bar often requires stronger evidence, specifically, a large study with long follow-up duration and additional confirmatory studies. In contrast, rapid adoption of more aggressive therapy may accelerate after a single positive trial. These trends are illustrated by the finding that the majority of older ER-positive women who undergo breast-conserving surgery continue to receive RT[15-17] despite a mature randomized trial demonstrating low rates of local recurrence and no survival difference when RT is omitted in this group.[18] Similarly, the finding in the ACOSOG Z0011 trial that axillary dissection could be eliminated in patients undergoing breast-conserving therapy with metastases in 1 or 2 sentinel nodes also engendered a wide variety of concerns regarding why this practice should not be adopted.[19] In contrast, bevacizumab received accelerated approval for use in metastatic breast cancer based on an improvement in progression-free survival, which subsequently did not translate into improved overall survival, and the therapy was associated with significant toxicity.[20]

The higher bar supporting less aggressive treatment also requires more certainty that an individual patient falls within the subgroup for which the treatment lacks benefit. Advances in personalized medicine have improved the accuracy of evaluative testing for management of systemic therapies in breast cancer. Figure 1 below illustrates the

impact of widely adopted tumor biology tests on the accuracy of the absolute net benefit of chemotherapy for patients with invasive breast cancer with favorable prognosis after treatment with locoregional and endocrine therapies. Before additional tumor testing, the average absolute net benefit in 10-year disease-free survival in this group is 4%.[21] Prior to the incorporation of HER2 and the 21-gene assay testing into treatment guidelines, recommendations from consensus panels for use of adjuvant chemotherapy in this patient population with favorable prognosis differed markedly.[22-26] The illustration assumes that all patients undergo HER2 testing and the 85 patients who test negative undergo 21-gene assay testing.[27-31] After completing the test strategy, one-quarter of patients (29 with average net benefit of 10% or greater) would receive a recommendation to commit to therapy and approximately half (46 patients with net benefit of less than 1%) would receive a recommendation to omit therapy. Indeed, an important contribution of the 21-gene assay test to the management of patients with favorable prognosis is that it can identify a subgroup of patients for whom the addition of adjuvant chemotherapy would confer no additional benefit.[32-34] Furthermore, the TAILORx trial[35] will further clarify with greater certainty the cut-point on the 21-gene assay score below which patients do not receive benefit from systemic chemotherapy.

Clarify the Outcomes Being Considered in the Examination Room

A third challenge for clinicians is the need to clarify the outcomes that are being considered in the examination room. It is difficult for patients to disentangle the probability and consequences of different outcomes of treatment, particularly disease recurrence versus death. Disease-free survival is a composite endpoint that includes locoregional and distant recurrence and may include new contralateral cancers. Patients often equate any recurrence with death and fear of recurrence strongly influences patient preferences for the most aggressive treatments.[36,37] However, the contribution of locoregional recurrence to total risk is nontrivial in patients with favorable prognosis. The risk of locoregional recurrence is largely determined by the underlying tumor biology and may not be altered with more aggressive locoregional therapy.[38-41] For example, patients with ER-, PR-, HER2-negative (triple-negative) breast cancer have the highest risk of locoregional recurrence regardless of whether they are treated with breast-conserving therapy[42] or with mastectomy and RT.[43]

Understanding the consequences of treatment on quality of life is another challenge. In general, patients report high quality of life after recovery from the treatment period, and quality-of-life consequences of treatment are well established.[44] However, an important yet poorly recognized outcome that can be confused with longer term quality of life is patients' immediate feelings about the treatment decisions themselves. Heuristics, ie, mental short cuts, strongly influence treatment decisions. These powerful gut responses drive patient preferences for the most aggressive treatment strategy because they focus attention on the overall threat of cancer rather than the benefits and harms of each treatment option. The most challenging example is anticipated regret ("if I were to get a recurrence I would feel better knowing that I did everything I could to avoid it"). A problem with this rationale is that people are poor predictors of their future emotional responses. Anticipated regret helps explain why many patients favor adjuvant chemotherapy even when the net benefit in 10-year disease-free survival is less than 2%.[45,46] The decision to undergo contralateral prophylactic mastectomy in patients who do not have elevated risk of a second primary tumor (those who do not have a BRCA test positive or 2 or more first-degree relatives diagnosed with breast cancer)[47,48] is another example of the potentially powerful role of anticipated regret.

REDUCING POTENTIAL OVERTREATMENT OF PATIENTS WITH FAVORABLE PROGNOSIS

Clinicians need a better understanding of how patients formulate preferences for treatment. In particular, clinicians need to be more cautious about how patients process quantitative information, because powerful factors limit the role of deliberative reasoning in formulating preferences for treatment, especially when the decision-making process is burdensome. Yet, clinicians are generally unaware of this influence and are poorly prepared to address it. Addressing heuristics in the examination room will be difficult because these intuitive mental processes are largely subconscious. However, some potential strategies include more clinician education and feedback, more time for patient deliberation, and deployment of decision tools to help focus patient's attention on net benefit of treatment rather than overall threat of disease.

Ultimately, the responsibility for minimizing overtreatment in cancer will lie largely in the hands of physicians. Indeed, physician's influence will likely increase as more patients fall under treatment guidelines based on stronger evidence and more accurate evaluative strategies. This is because rules imposed by clinicians that limit the range of treatment options available to patients is a

powerful constraint on potential overtreatment. Indeed, in breast cancer, evidence-based medicine combined with better evaluative tools have already had palpable effect on reducing the morbidity and burden of locoregional therapies.

The growing influence of physicians in treatment decision-making obligates scrutiny about how recommendations are formulated and conveyed to patients. It is particularly important to understand how clinical guidelines and consensus statements are developed and used because they will play an increasing role as personalized cancer medicine advances.[49] Guidelines strongly influence recommendations because they are authoritative, they simplify the decision process for both patient and physician, and they provide norms that diminish clinician concerns about the social consequences of treatment decisions. The translation of guidelines into the examination room is largely determined by the quality of the clinical information that is used to apply them to individual patients. Thus, there is enormous need to examine how tests are selected, the quality of test processing and reporting, and how results are interpreted and incorporated into treatment recommendations.

Finally, it is also important to examine and address physician attitudes that may predispose patients to overtreatment. Clinicians may overestimate the benefits of treatment based on inferences from experiences with their patients. This is a particular problem for patients with favorable prognosis, because most patients do well and the net benefit of the most aggressive treatment options is generally small.

Interdisciplinary clinician decision models may be powerful strategies to address the challenge of translating clinical information to treatment recommendations for individual patients. Tumor board review focuses attention on the validity and clinical utility of the evaluative information used to formulate the recommendations and can assure patients that recommendations are thorough, impartial, and evidence-based. Advances in communication and clinical database technology can now be harnessed to build innovative approaches to clinician decision support that can be used for more patients in order to optimally individualize cancer care.[50,51] More accurate evaluative strategies with test results incorporated into interdisciplinary decision models may minimize the potential for overtreatment in patients with favorable prognosis. Breast cancer will serve as a useful model going forward to examine to what extent advances in personalized medicine are translated into gains in health, one patient at a time.

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