Real Personalized Medicine

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Being a physician is complicated. After all, we are not fixing a broken car or other machine; we are trying to help another human being. In the treatment of patients with a curable malignancy, the need to balance maximizing cure rates against minimizing serious and sometimes lethal toxicities that often occur late in treatment is increasingly common. This balance is usually less of an issue in diseases in which cure is infrequent and survival is short. In this situation, trying to maximize cure rate is the overriding factor. However, in cancers in which the chance for cure is very high, particularly if second-line therapy also presents a possibility of cure, the situation is much more problematic.

Examples of the difficult decisions that physicians and patients must address can be found in early-stage Hodgkin lymphoma (HL) and of ductal carcinoma in situ (DCIS) of the breast. HL was a uniformly fatal disease until reports on the use of radiotherapy by early investigators, including Peters and Middlemiss,¹ Kaplan,² and Tubiana et al³ showed that some patients with relatively limited disease appeared to be cured. However, follow-up of these patients showed serious long-term toxicities associated with radiotherapy as it was then administered.^{4,5} Although median survival was extended with radiotherapy, most patients with HL eventually died of the disease. It was not until the combination chemotherapy regimen MOPP (mechloethamine, vincristine, procarbazine, and prednisolone) was used that experts noted a significant reduction in the number of deaths from HL.⁶ Subsequent studies showed that (1) adding an effective chemotherapy regimen to radiotherapy improved the cure rate, (2) the results seemed to be better with chemotherapy followed by radiotherapy in patients at high risk, and, more recently, (3) the use of chemotherapy alone was effective in patients with disease of all stages.

The ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) regimen generally does not cause infertility and has a small risk of secondary neoplasms. Investigators have shown equivalent survival in patients with early-stage, low-risk HL who experience a complete remission with a brief course of ABVD alone and with the same brief course of ABVD followed by involved-field radiotherapy.⁷ The chances of remaining continuously disease-free for 3 years was higher for patients who received radiotherapy (95% vs 91% with ABVD alone), with equivalent overall survival (97% vs 99%, respectively). The overall survival might eventually alter in favor of the group that received radiotherapy as a result of eventual death from lymphoma for some of the patients who experienced relapse, or may show an advantage for no radiotherapy because of the eventual impact of second cancers and vascular disease related to the radiation therapy. However, although the overall survival seems to be similar, a slightly higher relapse rate consistently seems to occur when radiotherapy is not administered.^{7,8}

Thus, the physician and patient are left balancing the advantage of no relapse (ie, avoiding psychologic distress, a potential bone marrow transplant, and the possibility of a slight decrease in survival) versus the benefits of avoiding radiotherapy (ie, reduced risk of a second cancer, reduced risk of cardiovascular disease, avoiding the acute toxicities of radiotherapy, and reduced cost of thera-

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py). Modern radiotherapy techniques seem to have reduced the long-term risks associated with radiation, but those risks remain greater than with no radiation.

A similar situation can be found in decisions regarding the management of DCIS treated with surgical excision. Patients treated with surgery alone have a local recurrence rate of 28% at 10 years, but adjuvant radiation therapy lowers the rate to 13%.⁹ No evidence of a survival difference is seen. Making the decision more fraught, 30% of women receiving adjuvant breast irradiation in good centers rate their cosmetic effect at fair to poor by 3 years.¹⁰ Any recurrence in that population leads to a recommendation of mastectomy, but patients who did not undergo radiation therapy are candidates for breast-conserving treatment should their disease recur.

No randomized trials comparing mastectomy with breast-conserving surgery plus radiation therapy in DCIS are available. Several studies compare local excision to local excision plus whole-breast radiation (with or without tamoxifen),⁹ and all showed improved local control with the addition of whole-breast radiation therapy. However, no studies were powered to assess the effect on survival. So the question to patients becomes, are you optimistic that you will be in the group that does not experience a recurrence? Or would you rather not live with the constant threat that recurrence or progression to invasive disease may occur? The decision becomes an emotional one because no data are available to guide it. We can't discern which patients will experience recurrence or progression and which will not.

In both diseases, the addition of radiation therapy to lower the recurrence rate will result in many patients receiving treatment with only a few receiving benefit from that treatment. What are you more afraid of: recurrence or the treatment to prevent recurrence? Like Clint Eastwood's character Harry Callahan said, you have to ask yourself, "do you feel lucky?"

Studies that compare treatments—and that would assist these decisions—can look for superiority (ie, that one treatment clearly has a better outcome), or for noninferiority (ie, that within preset statistical boundaries, it cannot be shown that one treatment is worse than another). The study by Radford et al⁷ notes the complexities involved in interpreting this information to make a treatment decision. Their study of early-stage HL comparing a brief course of ABVD versus a brief course of ABVD followed by radiotherapy in patients in remission was designed as a noninferiority study. However, the authors originally planned that if the patients receiving chemotherapy had a durable remission rate not more than 10% lower than those receiving chemotherapy and radiotherapy (ie, a difference that might not have been expected to translate in improved overall survival), the study would demonstrate noninferiority. However, after the study was started, the investigators decided to reduce the target for noninferiority to 7%.

As it turned out, the study showed that the 95% confidence limit was between 1.3% better and 8% worse progression-free survival for the chemotherapy alone arm. If the original 10% margin had been kept, this study would have shown noninferiority, but because of the change to 7%, the study did not meet the noninferiority margin. But which limit was correct: the first decision (in which case the 2 regimens would be considered noninferior to each other) or the second decision (that the progression-free survival of the chemotherapy alone arm missed the target for noninferiority)?

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Will the advent of precision medicine solve these dilemmas? Treatment choices such as these would not be so complicated if we had biomarkers to identify which patients with early-stage HL would be cured with ABVD alone and which would require radiotherapy. Because approximately 90% of patients with HL are cured with chemotherapy alone, we are actually looking for a way to identify the 4% or so of patients who require additional therapy. Similarly, if we knew which cases of DCIS would not relapse after local excision alone, determining which patients need radiotherapy would be easy.

Examples of cases in which we have this information are increasing. We have known for decades that patients whose breast cancers express estrogen receptors are likely to respond to hormonal manipulations, whereas patients whose tumors do not express hormone receptors will not benefit. Patients with acute lymphoblastic leukemia whose cancer has the Philadelphia chromosome and expresses BCR-ABL obtain great benefit from imatinib and similar drugs, but other patients with acute lymphoblastic leukemia do not benefit.^{11,12} Recently, we have seen that patients with non-small cell lung cancer (NSCLC) whose cancers have epidermal growth factor receptor rearrangements are likely to benefit from drugs such as erlotinib,¹³ and those with anaplastic lymphoma kinase rearrangements have a high likelihood of benefiting from crizotinib,¹⁴ but most patients with NSCLC benefit from neither drug.

Unfortunately, to date no equivalent markers are available to identify which patients with early-stage HL or DCIS can be safely treated with, respectively, a brief course of chemotherapy or local excision. In the case of HL, negative PET scan results after a brief course of chemotherapy indicate patients for whom observation might be reasonable, but even these patients show a slightly higher relapse rate if radiotherapy is not administered.⁷

In the case of DCIS of the breast, unifocality, smaller lesion size, and age older than 50 years are all signs of less risk of recurrence. Available genomic risk scores provide a low-risk indication for 60% to 70% of such women in addition to the standard clinicopathologic factors.

Who should make the decision, the physician? Presumably, the physician can be objective and is the most knowledgeable about the data. However, physicians also have potential conflicts of interest related to treatment decisions. Patients certainly have the right to make the decision. After all, it's their body. However, patients are more likely to be subject to optimistic bias, such as the mistaken belief that one's chances of experiencing a perceived negative event are lower than for other similar patients. Finally, the decision could be made by society. As health care costs increase, pressure to make treatments available based on cost-effectiveness is increasing. Of course, this requires assigning values to certain outcomes and determining the dollar amount of the outcomes.

In general, we believe that this should be the patient's decision, made in concert with an interested, caring, and informed physician. Not every patient will make the same decision. For some, the risk of relapse will be so terrifying that further therapy to minimize the risk of relapse will be desirable, despite attendant adverse events. Other patients will most fear the possibility of a second cancer or increased risk of coronary artery disease, or just fear undergoing radiotherapy. These patients will accept the already high chance of doing well with observation as the best option.

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If ever effective communication between physicians and patients is needed, it is during this decision-making process. This is certainly not a time to be looking at the computer rather than at the patient. This is also not something best done in a 12- to 15-minute office visit. The complexity of risk factors and the lack of proven survival benefit from adjuvant radiation are sufficient to demand an informed, compassionate physician who has time to listen to the patient's concerns and values. Communication is also not likely to be effective without a trusting and respectful relationship already in place. This is the sort of "personalized medicine" that effective physicians have been practicing since before the term became part of our medical vernacular.

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