of almost 30 years, 42% of the patients developed invasive breast cancer, and 22% died of breast cancer (Kaplan–Meier analysis). When I first looked at these figures, I thought they were quite high. An epidemiologist told me that, considering the long follow-up period, they were relatively low. Regardless of which position one takes, the study by Page et al. clearly shows that not all patients with untreated DCIS go on to develop invasive breast cancer. If these patients had had high-grade lesions, one would expect the percentage of invasive breast cancer and the breast cancer-specific mortality rate to be greater than those reported in this study, which consisted of only patients with low-grade DCIS (3,4), but it would certainly not reach 100%.

Dr. Atkin’s comments that the results with mastectomy are “so good” when compared with breast conservation. This is true when local recurrence is used as the endpoint of treatment failure. With mastectomy, one expects an extremely low local failure rate of approximately 1% (5). With breast conservation, depending on tumor size, margins, grade, etc., and on whether or not radiation therapy is used, local failure rates range from 10% to 40% (3,4,6,7). But if one uses the endpoint that really matters, breast cancer-specific mortality, no statistically significant difference by treatment has been reported by any group anywhere in the world. In the Van Nuys series, which consists of more than 700 patients, we have observed only five breast cancer deaths following a total of 73 local recurrences—an extremely low breast cancer-specific mortality. The mortality rate from breast cancer is so low in carefully followed DCIS patients that it will take an enormous prospective, randomized study to document any statistically significant differences based on treatment. Using our current data, I would estimate that the mortality rate after 10–15 years of follow-up would be approximately 1% for patients treated with mastectomy and approximately 4%–5% for patients treated with breast conservation (7).

Predicting local failure after breast conservation is difficult, but there are features that can be helpful. The size of the lesion and the adequacy of excision go hand in hand. The larger the lesion, the more difficult it is to adequately excise. The biology of the lesion is important. The more aggressive it is (higher grade), the more likely it is to recur and the more quickly it will probably recur. The genetics of the surrounding tissue may be important. Morphologically normal appearing tissue may already harbor the genetic changes necessary to develop DCIS or invasive disease at a later time. And, finally, treatment such as radiation therapy (and perhaps tamoxifen) is clearly important.

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References


Note

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Ms. Napoli makes a serious error when she refers to “off-label” drug prescription as the use of drugs “in instances when efficacy is unproved” (1). The U.S. Food and Drug Administration (FDA) is not in the business of cataloging all of the “proven” uses of drugs. Its responsibility is to determine that a drug is safe and effective for at least one indication before it can be marketed by a pharmaceutical company. Labeled uses are merely those that the FDA allows the manufacturer to state as indications based on the information provided by the manufacturer. The FDA’s authority is limited to monitoring the marketing practices of pharmaceutical companies. It has always, appropriately, left decisions about the proper uses of approved drugs to clinicians.

Unfortunately, many third-party payers share Napoli’s view. They do not understand that, if a drug is proven to be useful for a new indication, its labeling will not change to reflect that, unless the manufacturer decides to go to the substantial expense of presenting evidence to the FDA to request it. Furthermore, there are many instances in which a drug can be reasonably expected to be useful even in the absence of “proof.” An example of this situation involves the treatment of rare cancers. Extraluminal small-cell carcinomas share biologic and clinical features with their pulmonary counterparts and are therefore widely recognized to be appropriately treated with similar drug regimens (2). Likewise, bile duct carcinomas are histogenetically similar to pancreatic cancer and might be expected to respond to treatments that are effective for the latter tumor. Yet both of these scenarios are so rare that they will never be subjected to evaluation by randomized, controlled trials. Furthermore, they would be unlikely to head any pharmaceutical company’s list of priorities for obtaining approval for FDA labeling.

When I prescribe a drug for a nonlabeled indication, it is always because of scientific evidence supporting its use. I have no qualms about using my judg-
ment to determine what evidence is sufficient to present to my patients for their consideration. Limiting my patients’ choices to those indications that are economically feasible for a pharmaceutical company to submit to the FDA is neither appropriate nor fair.

I am sure that my patient with small-cell carcinoma of the pancreas, who is now in complete remission after chemotherapy with cisplatin and etoposide, could convince Ms. Napoli to understand her error. My Medicare carrier is, unfortunately, a more difficult case, but I am hoping that common sense will prevail. 

CARL D. ATKINS

References


Note

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Response

Dr. Atkins rightly identifies circumstances in which a drug with proven efficacy is not put through the FDA-approval process. Off-label use of antineoplastic drugs, however, includes a wide variety of possibilities. And the scientific evidence to support these uses can range from zero to extensive. In defending off-label prescribing, Dr. Atkins’ choice of words is revealingly vague, e.g., “reasonably expected to be useful,” “widely recognized,” and “might be expected to respond.” Furthermore, he seems to have missed my point about the importance of informed consent. My letter to the editor was written in response to a Journal of the National Cancer Institute News report on a survey designed by the American Enterprise Institute and the American Cancer Society (1). We do not know whether other oncologists have Dr. Atkins’ self-described high standards. The designers of this National Survey of Oncologists on Off-Label Prescribing failed to question physicians about whether they inform their patients regarding this common practice (2). I do not object to off-label prescribing, but the important questions are these: Are patients informed when the supporting data for off-label drug use can best be described as weak, phase II, a “guessedimate,” or nonexistent? Are the expected side effects explained?

As for the anecdotal evidence Dr. Atkins offers about his patient with pancreatic cancer, it raises even more questions that should have been included in the survey: How many oncologists tell their patients the true meaning of the word “respond”? How many oncologists explain the difference between “response rate” and “durable remission”?

MARYANN NAPOLI

References


Note

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Re: Cure of Helicobacter pylori Infection and Duration of Remission in Low-Grade Gastric Mucosa-Associated Lymphoid Tissue Lymphoma

The recent report by Neubauer et al. (1) and the accompanying editorial by Roggero et al. (2) both speculate on the likely sequence of events responsible for the development of histologic transformation in patients with initially low-grade mucosa-associated lymphoid tissue (MALT) lymphoma. Neubauer et al. support a sequential model, where loss of dependence on T-cell-derived factors is a necessary prerequisite for subsequent histologic transformation. This model is based on the finding of occult foci of high-grade lymphoma in gastrectomy specimens from four patients with persistent low-grade MALT lymphoma despite eradication of Helicobacter pylori. While consistent with previous proposals (3) and an earlier report of similar findings (4), this conclusion is based on the assessment of a biased sample and assumes the absence of such foci in patients who subsequently responded to anti-Helicobacter therapy. The single published study that systematically searched for the presence of occult foci of high-grade disease in gastrectomy specimens from patients with an endoscopic diagnosis of pure low-grade gastric MALT lymphoma found no instances of these foci in the five specimens examined (95% confidence interval = 0%–52%) (5). However, the reported finding of areas of divergent histology on repeated endoscopic assessment in 15% of all patients referred to a specialist center with previous endoscopic biopsies containing only low-grade disease suggests that the true incidence may be substantial (6).

In the absence of prospective studies of isolated anti-Helicobacter therapy in patients with known high-grade gastric MALT lymphoma, the lack of in vitro proliferation of cells from two cases of high-grade gastric lymphoma in the presence of autologous lymphocytes and heat-inactivated Helicobacter reported by Hussell et al. is often cited as evidence for the antigen independence of high-grade disease (7). A number of recent reports confirming objective regression of unequivocal high-grade gastric lymphoma following isolated anti-Helicobacter therapy (8–10) establishes that some histologically aggressive gastric lymphomas do remain dependent on antigen-induced, T-cell-derived factors. Thus, the sequential model proposed must be modified to incorporate these observations. The frequency of this sequence of events and its implications for the possible cytokine dependence of transformed lymphomas in other sites remain undetermined.

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References