Reframing treatment for ductal carcinoma in situ: Could less be more?

In a typical breast surgery practice, nearly one-fifth of new patients present with ductal carcinoma in situ (DCIS), usually detected on mammography as an incidental finding. Most of these women are otherwise healthy, take care of themselves, have had a mammogram as part of their routine health maintenance, and are now grappling with a “cancer” diagnosis. When explaining to patients that DCIS generally has a favorable outcome and that it rarely affects mortality, it always becomes apparent that medical and surgical professionals still have more questions than answers regarding this disease. Is DCIS cancer or not? What would happen if no treatment for DCIS were available—if patients had to wait until they developed invasive cancer before choosing to have surgery? And how do we have a conversation with patients so that we can reduce the anxiety that often motivates these women to choose a bilateral mastectomy for a noninvasive disease?

Additional research

DCIS is one of the earliest examples of a significant unintended consequence arising from population-based screening. Since mammography was introduced in the early 1980s, the incidence of DCIS has increased from a rarely encountered diagnosis to nearly 50,000 new cases in 2011.1 The cornerstone of treatment assumes that all occurrences of DCIS could become invasive if left untreated. Although clearly some high-grade, extensive DCIS could become invasive, it is difficult to predict how often and how soon this process is likely to happen in an individual patient.

Studies based on current incidence rates of DCIS and invasive cancer have shown that less than half of DCIS cases become invasive cancer.2 If these patients could be identified before recommending treatment, many women could be safely managed with observation, similar to patients with other known risk factors for breast cancer, such as atypical ductal hyperplasia (ADH) or a breast cancer mutation.

A related biologic question is whether some occurrences of DCIS can revert from DCIS to ADH, and, if so, whether some low-risk DCIS cases may be safely managed with either systemic therapy or active surveillance alone. Preliminary research has shown that short-term, preoperative endocrine manipulation for DCIS reduces cell proliferation with reversion to ADH in some patients, but whether this strategy is sufficient for long-term management is a topic still undergoing active research.3,4 In the very near future, molecular markers may allow for more reliable identification of this low-risk group.5-7

**CALGB 40903**

Cancer and Leukemia Group B (CALGB) 40903 is a recently activated Alliance study that will determine which subsets of ER(+) DCIS might be most amenable to systemic treatment. It is a single-arm trial for postmenopausal women with hormone receptor positive ER(+) DCIS, who will be monitored during six months of preoperative endocrine therapy while being treated with an aromatase inhibitor (AI) (letrozole, 2.5 mg PO QD).

Response to neoadjuvant therapy will be assessed by imaging endpoints, with change in magnetic resonance...
imaging tumor volume as the primary endpoint of the study. However, an important goal is to look for pathologic changes in the DCIS, with molecular studies planned to identify biomarkers predictive of response to endocrine therapy.

A quality of life companion study has been embedded into the trial to assess frequency and severity of side effects associated with neoadjuvant hormonal treatment, as well as how these symptoms affect treatment adherence. Women most likely to benefit from participation in this study are those who, because of the extent of the disease, are borderline candidates for lumpectomy. If, as in neoadjuvant studies for invasive cancer, overall tumor size is reduced, some women with DCIS may be better lumpectomy candidates after AI treatment.

Although the trial is designed to include surgical excision at six months, the study will lay the groundwork for future trials of DCIS management that reserve surgical excision for only those patients at highest risk for invasive progression. Such trials are already under way for patients diagnosed with pancreatic intraductal papillary mucinous neoplasm and early prostate cancer.

The long-term clinical objective of these studies is to reduce the consequences of over-diagnosis by making locoregional treatment a targeted therapy for those patients who would benefit most. It is expected that such research will yield important insights into early cancer biology. Clinical trials in DCIS will answer which options, including nonsurgical ones, may be safely recommended to patients.

References