half had a relapse after cessation of therapy. Only 8% in the control group showed a "response."

Serologic and tissue markers for antigens associated with hepatitis C have not yet been developed, so it is difficult to diagnose hepatitis C with certainty. An antibody directed against one or more antigens from the C virus will soon be released for general use. Until then, the diagnosis of hepatitis C remains presumptive, based on exposure to blood or blood products. It is a mistake to assume that all cases of chronic hepatitis without B markers represent hepatitis C. The diagnosis should be considered only in patients with suitable epidemiologic risk factors (and those who test positive for the C antibody when this test becomes available).

SIDE EFFECTS

Side effects are frequent with interferon. Most are not serious and are reversible with dosage reduction or cessation of therapy. Flulike symptoms, including muscle and joint aches, fatigue, nausea, and malaise, develop in most patients and usually abate after a week or two. Leukopenia may occur and, if unrecognized, can be serious in the event of bacterial superinfection. This is rare at the dosage used for treatment of hepatitis. Depression may be severe, and is most likely to be troublesome in patients with a history of depression. Diarrhea may occur in one third of treated patients and mild alopecia in nearly one fourth. Hypo- and hyperthyroidism have recently been described in hepatitis patients treated with interferon. Whether this is caused by the drug or is merely a coincidence is unknown.

UNRESOLVED ISSUES

Opinion is divided regarding the wisdom of wide-scale use of these drugs outside of a research setting. Interferons are expensive and their administration is cumbersome. Although the drug should not be withheld if it appears to be indicated, it is probably best to refer these patients for treatment under research protocols. If none exist, it is justifiable to make this treatment option available to the patient, although interferon therapy is best monitored by a gastroenterologist or a hepatologist.

The dosage and duration of therapy are unsettled. Studies that use higher dosages have higher success rates, and longer courses of therapy appear to be superior to shorter ones. Retreatment schedules for those who relapse after therapy are just now being settled. Although retreatment appears to be successful, its duration and cost remain sources of concern. The long-term benefits also are unknown. It will be many years before we know whether interferon therapy is associated with fewer complications, including cirrhosis, decompensated cirrhosis, hepatoma, and death or need for transplantation.

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MILESTONES IN THE TREATMENT OF BREAST CANCER

Today's treatment of breast cancer reflects our improved understanding of tumor biology. The principles of treatment have evolved from the "Halstedian" concept of tumor growth to consideration of breast cancer as a systemic disease at its onset. Accordingly, we treat the regional as well as the systemic disease, with new appreciation for the value of adjuvant chemotherapy.

Early detection of any malignancy, including breast cancer, has a positive effect on survival. Periodic breast self-examination (BSE) is associated with a lower probability of positive axillary nodes at the time of diagnosis (47% *v* 63%), lower probability of distant metastases (2.7% *v* 14.6%), smaller tumors (2.5 cm *v* 3.3 cm), and improved 5-year survival (75% *v* 57%). The survival advantage remains even after we account for "lead-time bias," whereby early clinical detection of cancer can give the appearance of improved survival.

Mammography detects smaller cancers (32% less than 1 cm, Breast Cancer Detection Demonstration Project [BCDDP]), which have a lower probability of positive axillary nodes (20%, BCDDP); this translates into lower mortality (30% in the breast screening project of the Health Insurance Plan of Greater New York).

These data led the American Cancer Society to recommend the following for breast cancer screening: monthly BSE after age 20; examination by a physician every 3 years between ages 20 and 40 and every year after age 40; baseline mammography between ages 35 and 39; and screening mammography every 1 to 2 years

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between ages 40 and 49 and annually after age 50.

AXILLARY DISSECTION IS KEY

Surgical extirpation, once the sole treatment for primary breast cancer, now plays a complementary role. In the early 1970s, the results of modified radical mastectomy, total mastectomy with or without radiation, and Halsted's radical mastectomy were compared. The three procedures did not differ significantly in overall and disease-free survival. The comparison demonstrated the value of axillary node status with regard to staging and subsequent adjunctive therapy, and axillary node dissection became an integral part of all mastectomies.

The value of axillary dissection was reaffirmed in the mid-1970s, when partial mastectomy with axillary dissection and radiation therapy was compared with radical mastectomy in patients with small cancers of the breast. Again, there was no difference in disease-free and overall survival. At this time, the Cleveland Clinic reported similar survival statistics in patients with small favorable cancers who were treated with partial mastectomy, axillary dissection, and no radiation therapy.

The late 1970s saw the advent of plastic reconstruction of the operated breast. The timing of the reconstruction relative to the mastectomy and its effect on subsequent surveillance for local recurrence are important issues. Several series have shown that immediate reconstruction can be performed safely in selected patients (ie, those who have tumors smaller than 5 cm and clinically negative axillary nodes). Reconstruction does not significantly delay the administration of adjuvant chemotherapy or radiation therapy. Immediate reconstruction also does not mask local recurrence, which occurs in 2%. No decreased survival is evident following immediate reconstruction, and patients are satisfied with the cosmetic results.

CHANGING PROGNOSTIC INDICATORS

Assessing the results of systemic adjuvant therapy for high-risk breast cancer has been a major research effort in the last 15 years, as more has become known about prognostic indicators. The primary indicator is the degree of axillary nodal involvement. Survival worsens as more nodes are involved, especially four or more. Tumor size and the status of estrogen receptors also are predictive. Relapse is more likely and overall survival is poorer with larger tumors, estrogen receptor-negative tumors, and more active, aggressive tumors.

The National Institutes of Health Consensus Development Conference in 1985 recommended combination chemotherapy for premenopausal women with positive axillary nodes and tamoxifen for postmenopausal women with positive axillary nodes and positive estrogen receptors. Although unable to state with certainty that adjunctive therapy would benefit the other subgroups, the conference recommended that treatment be considered for high-risk patients. Cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) appears to be the most effective regimen with the lowest toxicity and has become standard adjunctive therapy.

Node-negative breast cancer is believed to have a favorable prognosis, but the fact is that 20% to 30% of these patients eventually have recurrences and ultimately die of metastases. The Consensus Conference of 1985 did not have enough data to conclude that these patients would benefit from adjunctive treatment; but in May 1988, the National Cancer Institute issued a clinical alert regarding the preliminary results of three ongoing trials involving patients with node-negative cancer. Although the median follow-up was only 3 to 4 years, adjuvant systemic therapy had resulted in statistically significant improvement in disease-free survival in all three studies. A controversy then arose: Should all node-negative patients receive adjunctive therapy or is there a way to select those most likely to benefit?

Along with axillary nodal involvement, tumor size, and hormone receptors comes a potential "second generation" of prognostic indicators. Thymidine labeling and flow cytometry can determine the proliferative capacity of the cell. A higher thymidine labeling index, greater degree of anaploidy, and higher percentage of S fraction correlate with a higher rate of recurrence.

The development of these "second-generation" prognostic indicators may lead to better identification of patients with good prognoses, and spare them systemic adjuvant therapy while identifying with more certainty those patients who will benefit.

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