Consensus in Medicine

Adjuvant chemotherapy of breast cancer

SUMMARY OF AN NIH CONSENSUS STATEMENT

A consensus development conference on adjuvant chemotherapy of breast cancer was held at the National Institutes of Health on 14-16 July 1980. Its purpose was to bring together practising physicians, research scientists, consumers, and others in an effort to reach general agreement on the concepts and results of adjuvant chemotherapy trials in breast cancer and their implications for medical practice.

A consensus development panel met to consider, together with members of the audience, the questions presented below. The members of the panel included a patient and representatives from the many disciplines concerned in evaluating and treating breast cancer. The panel met after formal presentations and discussions to assess the issues based on the evidence presented. This summary is the result of its deliberations.

Introduction

Adjuvant chemotherapy of breast cancer means the use of cytotoxic drugs after primary therapy. The rationale for adjuvant chemotherapy is to eradicate occult metastatic disease which otherwise would be fatal. The assessment of adjuvant chemotherapy must balance efficacy against toxicity. The basic measure of therapeutic benefit is patient survival with an acceptable quality of life.

Primary breast cancer is a heterogeneous disease with varying potentials for metastatic relapse and response to adjunctive drug therapy. Currently, three critical variables are used in planning adjuvant chemotherapy trials: involvement of the axillary lymph nodes, menopausal state, and oestrogen receptor levels. Three axillary lymph node categories are commonly accepted as prognostically important: negative axillary nodes, one to three positive axillary nodes, and four or more positive nodes. These three categories strongly predict the risk of relapse after appropriate local treatment.

These three nodal subsets, when combined with the menopausal status (premenopausal or postmenopausal and oestrogen-receptor status (positive or negative), result in 12 prognostic subsets. These subsets form the basis for planning additional clinical trials, and only from these trials will the best strategy for improved patient care emerge. Adequate analysis of a trial of adjuvant chemotherapy must consider whether enough data exist for one or more subsets to establish the role of that trial in assessing—and possibly modifying—current medical practice.

In general, the merits of a new or modified adjuvant treatment regimen must be assessed through comparative clinical trials which randomly assign patients to alternative treatments. Such a design helps to ensure that patients in each of the treatment groups are comparable.

If a clinical trial is to yield meaningful information, patients need to be followed for a sufficient period, so that long-term results may be evaluated. No simple standard for duration of follow-up can be set, because the importance of observed results depends on the nature of the group of patients under study. For example, to provide meaningful information, patients with minimal, potentially curable disease have to be followed for a much longer time than do patients with advanced disease.

There are two types of toxicity associated with chemotherapy: acute and remote. The acute adverse effects relate to the immediate drug administration. Remote adverse effects, which may also be chronic, may occur long after drug administration has ceased. Acute toxicities include bone marrow suppression, nausea and vomiting, loss of appetite, weakness, mouth ulcers, and hair loss. The remote chronic effects to which the physician should be alerted include organ damage, such as doxorubicin (adriamycin)-induced cardiomyopathy, sterility, and the induction of second cancers due to the carcinogenic potential of some of the drugs used.

The length of time during which the patient is free of disease after treatment is important but often must be regarded as only a preliminary indication of therapeutic results. The ultimate efficacy of treatment must be measured in terms of survival time, although the quality of survival must be taken into consideration.

Studies that report negative results—that is, no significant differences—should not be regarded as failures. If the study initially posed important question(s), and the study was designed and executed properly, then any negative finding is an important contribution to knowledge.

It is desirable to examine the possible influences on therapeutic results by factors not anticipated in the original study design. A cautionary note is in order, however: retrospective observations based on small subgroups of patients may be misleading.

By definition, adjuvant chemotherapy is drug treatment added to adequate local excisional therapy. The adjuvant chemotherapy trials reported to date have used radical or modified radical mastectomy. Future trials may use less radical surgical procedures, but the impact of lesser surgery on adjuvant chemotherapy remains to be determined.

In breast cancer treatment a key prognostic determinant for the use of adjunctive therapies and their results is the state of the axillary lymph nodes at the time of primary treatment. A satisfactory dissection of the axillary nodes and histopathological evaluation is essential for accurate staging.

With these precepts underlying their discussions, the panel addressed the following questions and came to the following consensus.

Members of the consensus development panel were: Dr Stephen K Carter Northern California Cancer Program, Palo Alto, California (chairman); Dr George P Canellos, Sidney Farber Cancer Institute, Boston, Massachusetts; Ms Barbara E F Chambers, Washington, DC (consumer representative); Dr Sidney J Cutler, Georgetown University, Washington, DC; Dr Edwin R Fisher, University of Pittsburgh, Pittsburgh, Pennsylvania; Dr Robert W Frelick, Association of Community Cancer Centers, Bethesda, Maryland; Dr Walter Lawrence, jun, Chairman, Commission on Cancer, American College of Surgeons; Dr Theodore L Phillips, University of California Medical Center, San Francisco, California; Dr Hiram C Polk, jun, University of Louisville Health Sciences Center, Louisville, Kentucky; Ms Connie Henke Yarbro, Oncology Nursing Society, Columbia, Missouri. The programme co-ordinator for the conference was Dr Daniel G Haller, National Cancer Institute, National Institutes of Health, Bethesda, Maryland.

(1) Have clinical trials established the efficacy of adjuvant chemotherapy of breast cancer?

Despite positive and encouraging findings from clinical trials, the answer to this question must remain qualified. The value of adjuvant chemotherapy, in terms of a demonstrated increase in survival of treated patients, has been established with any degree of certainty only for a select group of patients with breast cancer.

Premenopausal patients with histological evidence of lymph node metastases who have undergone local treatment by mastectomy have experienced an increase in disease-free and overall survival after adjuvant chemotherapy with established combination regimens. Adjuvant chemotherapy now appears indicated for this defined subset of patients.

Since the optimal adjuvant therapy for the premenopausal patient with lymph nodal metastases has not yet been developed, continued clinical investigations are indicated. If entry into a well-planned clinical trial is not feasible or acceptable to patients in this specific group, adjuvant combination therapy is indicated. Regimens which have proved efficacious in recognised clinical trials should be selected. The treating physician is responsible for evaluating the results of these trials for efficacy and toxicity.

Adjuvant combination chemotherapy, with agents shown to be active in treating advanced breast cancer, has been shown to be more effective than chemotherapy with a single agent. Current information suggests that these drugs should be given at full dosage and for prescribed durations, since lesser amounts of chemotherapy or changes in schedule have shown inferior results.

In combination with adjuvant chemotherapy of stage II disease, adjuvant radiotherapy has not provided significant increases in survival, although it has reduced chest wall and regional lymph node recurrence in some studies.

(2) Do the benefits of adjuvant chemotherapy clearly outweigh the risks?

Various forms of early toxicity have been documented in regimens that have proved to be therapeutically effective. Late effects of the various drug programmes have not been fully identified. The survival benefits in premenopausal patients with histological evidence of lymph node metastases (stage II) appear to outweigh the disadvantages of early toxicity.

Psychological and socioeconomic problems resulting from adjuvant chemotherapy have been identified as risks, in addition to the direct toxic effects of drugs, but they have not been quantitatively defined. In the meantime, education, counselling, and emotional support of the patient by the cancer treatment team are of utmost importance. An increased financial burden to the patient, interruptions in family life and occupation, and changes in body image may accompany the use of chemotherapy. This panel believes that these problems should be investigated prospectively and addressed directly in future conferences.

(3) Should future adjuvant studies include hormonal manipulations?

Studies of hormonal manipulation as adjuvant therapy for breast cancer have suggested that such treatment produces benefits, but the results are not definitive when judged in terms of survival. Current studies on oestrogen-receptor status are yielding more reliable data on the value of hormonal manipulation in the context of adjuvant treatment. The problems that exist in assessing these data include determining the relative roles of hormonal and chemotherapeutic treatments, the significance of the hormonal effects of the chemotherapeutic agents, and the reliability of the receptor assays in individual patients. For now, it appears that no hormonal manipulation has been established with enough confidence to make hormonal alterations—either alone or with chemotherapy—a standard form of adjuvant therapy. Recent data regarding potential benefits for hormonal treatment in patients who show significant oestrogen-receptor activity are encouraging.

Oestrogen-receptor activity should be measured routinely in all patients with breast cancer. In all adjuvant trials, particularly those entailing the use of hormonal treatment, oestrogen-receptor activity is an essential factor for classifying patients in planning the design of the clinical trial.

(4) What is the role of adjuvant chemotherapy in Stage I patients?

Patients with histopathologically negative axillary lymph nodes have a good prognosis after appropriate local treatment. The five-year disease-free survival without adjuvant chemotherapy may be expected to be at least 80%. The use of adjuvant chemotherapy in stage I patients exposes all to risks of toxicity without possible benefit to the majority. Some relevant studies are under way, but no conclusive clinical research data exist to support the routine use of adjuvant chemotherapy in these patients. Clinical research is now in progress to determine whether it is possible to identify a subset of patients with negative axillary nodes who are at high risk of relapse after primary therapy.

(5) What is the role of adjuvant chemotherapy in postmenopausal patients?

Recent analyses of some continuing studies of adjuvant chemotherapy seem to show early benefit in disease-free survival in one or more subsets of postmenopausal patients with positive axillary nodes. The preliminary nature of this information precludes a definitive statement about the role of such treatment. Clinical investigations should continue to explore the role of adjuvant chemotherapy in postmenopausal women with positive axilary nodes. Broad acceptance of the results of such trials would require concurrent controls who received only surgical treatment. Postmenopausal women with oestrogen-receptor-positive tumours may benefit from the adjuvant administration of relatively non-toxic hormonal treatment in combination with cytotoxic drugs. It appears logical that hormonal therapy and chemotherapy should continue to be explored in oestrogen-receptor-positive postmenopausal women, but only within the setting of well-controlled clinical trials.

Current information indicates that it might be necessary to give multiple drug regimens at full dose to achieve clinical benefit. Retrospective evaluation of patients in one large trial now seems to show increased survival for those postmenopausal patients who ultimately received the maximum prescribed dosage in contrast to those who received lower dosage.

Optimal treatment

Adjuvant chemotherapy of breast cancer is a rapidly changing and progressing subject. New concepts have emerged from large, complex clinical trials. But women with breast cancer and doctors need to understand that definitive answers do not exist for the best management of all aspects of this complex disease. The optimal approach to decision-making and treatment is multidisciplinary, within the framework of knowledge provided by current research. Because chemotherapeutic drugs are toxic, they should be administered only by or under the supervision of a doctor experienced in their use. Optimal care requires frank and open communication between the doctor and patient about the options available and the variables which make up the patient's potential prognosis, both for the risk of relapse and for response to therapy.

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