characterisation of the biochemical defect—for example, by functional studies in vitro with the protein incorporated into artificial membranes. Finally, it may be possible to correlate specific mutations with the clinical phenotype. Already the haplotypes at loci cosegregating with cystic fibrosis have been associated with the presence or absence of pancreatic insufficiency.[6]

The earliest impact of the new genetic information is likely to be on screening for the heterozygous carrier state. The implications of rapid advances in knowledge for screening in cystic fibrosis have been reviewed recently.[7] While some have suggested that carrier screening should be made available now—even though some 30% of cystic fibrosis chromosomes cannot be detected[8]—others favour waiting until more if not all of the mutations are known.[5,9] Clearly, before large scale population screening is undertaken a realistic assessment needs to be made of the likely demand in order to determine the facilities that will be required and so their cost. Though several studies in cystic fibrosis and other genetic diseases have shown that most people at risk say that they are in favour of screening,[10] the actual take up rate in some studies of patients at risk of Huntington's chorea has been as low as 13-16%.[11] A reasonable compromise, therefore, may be to offer carrier detection only to members of cystic fibrosis families and their partners.

Patients with cystic fibrosis and their families are also anxious to know about the therapeutic implications of the identification of the gene. In theory the abnormally functioning protein could be replaced—by either gene or protein therapy—or its defect restored to normal by drugs. Though techniques exist for gene delivery and human genes can be expressed relatively stably and in a lineage specific fashion in mouse bone marrow cells.[12] The selective introduction and expression of DNA in human epithelial cells seem to require an additional order of complexity. Moreover, as the cystic fibrosis gene product is a member of a family of related transmembrane proteins the selectivity of pharmacological intervention may also prove a problem. The therapeutic impact of the new knowledge may, therefore, not be felt for many years. Though we should continue financial support for these potentially exciting developments, we should not allow all the resources to be diverted at the expense of improving existing lines of treatment.

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Regular Review

Node negative breast cancer

Adjuvant chemotherapy should probably be reserved for patients at high risk of relapse

Patients with breast cancer and negative axillary nodes are not routinely given adjuvant systemic treatment after primary surgery. These patients, whose tumour seems to be confined to the breast, have a good prognosis without such additional treatment. Nevertheless, a clinical alert issued in 1988 by the National Cancer Institute suggested that all patients with breast cancer, regardless of axillary node disease, should now be considered for adjuvant treatment.[1] If widely adopted such a policy would have major implications for the management of patients with breast cancer. It is important, therefore, to review our current understanding of the clinical course of node negative breast cancer and the possible impact on it of adjuvant treatment.

Some 50-60% of all new patients with breast cancer have node negative disease, amounting to over 12 000 patients each year in Britain.[2] The proportion of such patients is likely to rise with the availability of screening programmes, which allow the disease to be detected at an earlier stage. Though most patients with node negative disease have a good prognosis, 20-30% will develop distant metastases and will ultimately die of their disease.[3] Adjuvant treatment might reduce the number of patients whose disease recurs. Before such treatment is offered to all patients, however, several questions should be asked (box).

Prognostic factors

To be of general use a prognostic factor should be easily measurable, give reliable and reproducible results, and allow wide separation of prognostic groups. For patients with node negative breast cancer no one factor satisfies all these criteria. A clear consensus has not emerged on how best to identify patients at high and low risk. The tumour characteristics that have been examined in most detail for prognostic importance include size, histopathological features, oestrogen and progesterone receptor characteristics, measurements of proliferative activity, and tumour ploidy.

The relation of the size of the tumour to relapse free survival and overall survival is well defined for patients with breast cancer and positive nodes but is less certain in patients with node negative disease.[4] The results of two large studies suggest that the prognosis worsens as the size of the tumour increases, but the effect on survival is small.[2,5] The size of the tumour has the advantage of being easy to measure. The same

does not hold true for histopathological grade: interobserver variability is high in grading tumours.[6] A recent study of over 1000 patients with node negative disease found that those with well differentiated tumours had a better relapse free survival and overall survival, with an improvement in outcome at five years of about 16% and 14% respectively over those with poorly differentiated tumours.[7] Such differences are impressive but have been achieved under ideal conditions with all the tumours graded by one expert histopathologist. Such prognostic information cannot easily be applied to the general population of patients.

The influence of oestrogen receptor state on survival in node negative disease has recently been reviewed.[7] Though there is a consistent trend for patients with oestrogen receptor positive tumours to have a longer relapse free survival, this failed to achieve statistical significance in many reports. When the improvement was significant it was usually small. Oestrogen receptor state alone is thus unlikely to select a group at high risk of recurrence. Most reports on progesterone receptor state in these patients suggest that it adds little information either independently or in combination with oestrogen receptor state.[8]

The proliferative activity of tumours can be measured by the thymidine labelling index or by DNA flow cytometry. Patients whose tumours have a low thymidine labelling index have a better prognosis, with an improvement in relapse free survival at five years of 15-23%.[9,10] The thymidine labelling index is, however, cumbersome to measure, must be performed on fresh tissue, and is not widely available. DNA flow cytometry, on the other hand, is an automated technique that can be applied to tissues which are fresh, frozen, or embedded in paraffin. It provides information not only on the proliferative activity of a tumour, by estimating the percentage of cells in the synthetic phase of the cell cycle (S-phase fraction), but also on the DNA content (ploidy). Though its prognostic significance in breast cancer has been investigated, few reports have focused exclusively on patients with node negative disease. Clarke *et al* reported that patients with diploid tumours and low S-phase fraction had a relapse free survival at five years of 90%, compared with 70% for those with diploid tumours and high S-phase fraction.[11] The S-phase fraction was not an important additional predictor of relapse free survival for patients with aneuploid tumours.

Though it is important to determine the effect of different prognostic factors, many of them are interrelated. In particular, there is a well established association between the absence of oestrogen receptors and poor tumour differentiation.[12] Tumour grade is also closely related to proliferative activity as measured by S-phase fraction[13] or thymidine labelling index.[14] Multivariate analysis may help determine the relative prognostic importance of these factors, but few analyses have included all the variables. Nevertheless, tumour grade and a measurement of proliferative activity seem to be emerging as having more prognostic importance than oestrogen receptor state.

Adjuvant chemotherapy

Trials of adjuvant chemotherapy for patients with node negative breast cancer may be divided into two groups: those in which the treatment was given at the time of, or very shortly after, primary surgery and those in which a more prolonged course of postoperative chemotherapy was used.

The Scandinavian study of perioperative chemotherapy showed persistent improvement in both relapse free survival and overall survival over 20 years for patients who received chemotherapy.[15] Two more recent studies with larger numbers of patients but short follow up also showed improvement in relapse free survival for those receiving chemotherapy but no difference as yet in overall survival.[16,17] This improvement in relapse free survival, while statistically significant, is small. In the Ludwig V trial, for example, the relapse free survival at four years increased from 73% for those patients who received no adjuvant treatment to 77% for those receiving cyclophosphamide, methotrexate, and fluorouracil.[16] This reduced relapse rate was confined to locoregional recurrence with no impact on the development of distant metastases.

- Is it possible to identify a group of patients at sufficiently low risk of relapse for adjuvant treatment to be unnecessary? Conversely, can a high risk group be identified in whom such treatment might best be justified?
- What is the evidence that patients with node negative disease derive any substantial benefit from adjuvant endocrine or cytotoxic treatment?
- What are the potential physical and psychological adverse effects of such adjuvant treatment?
- Using this information, can we define groups of patients for whom the benefits of treatment are likely to outweigh the costs?

Studies examining the efficacy of more prolonged adjuvant chemotherapy may be subdivided into two main groups: those in which all patients with node negative disease, regardless of the presence or absence of other prognostic factors, were included; and those in which only a subgroup of patients believed to be at high risk of recurrence was treated. The studies in which all patients were included have used a wide variety of cytotoxic drug combinations, and no consistent results have emerged.[18-21] The studies in which patients were selected for treatment examined the effect of chemotherapy on patients with oestrogen receptor negative tumours, although the Intergroup study also included patients with large ($\geq$3 cm) oestrogen receptor positive tumours. Different treatment regimens were used in all studies. The Milan group, using 12 courses of a combination of cyclophosphamide, methotrexate, and fluorouracil in patients with oestrogen receptor negative disease, found significant improvement in four year relapse free survival and overall survival in patients receiving chemotherapy.[22] The importance of this finding is difficult to interpret because patients in the control arm had an unexpectedly poor relapse free survival, with 21 of 45 patients having suffered a relapse at four years. Two large studies using 12 courses of methotrexate and fluorouracil[23] or six courses of cyclophosphamide, methotrexate, and fluorouracil combined with prednisolone[24] showed significant improvement in relapse free survival but not in overall survival at three to four years. The improvement for the patients receiving chemotherapy in these studies was 10-15%.

Adjuvant endocrine therapy

Two large studies of adjuvant tamoxifen in breast cancer have included patients with node positive and node negative disease. The Nolvadex adjuvant trial organisation study, which included 605 postmenopausal women with node negative disease randomised to receive either tamoxifen for two years or no treatment, reported an improvement in relapse free survival for patients given the antioestrogen.[25] This benefit was largely confined to those patients with moderately well differentiated (grade 1 or 2) tumours, with

negligible effect in patients with poorly differentiated (grade 3) tumours.[26] This finding, if confirmed, might have important implications for the use of tamoxifen, with the possibility of histological grade being a better predictor of benefit than oestrogen receptor state. The Scottish study, in which patients received tamoxifen for five years or no adjuvant treatment, found fewer relapses and deaths in both premenopausal and postmenopausal patients with node negative disease who were receiving adjuvant treatment.[27]

The National Surgical Adjuvant Breast Project trial B-14 is the only large study that has specifically examined the effect of adjuvant tamoxifen on patients with node negative oestrogen receptor positive tumours. After a median follow up of four years an improvement in relapse free survival of 5% was seen. This benefit was observed in both premenopausal and postmenopausal patients, but a survival advantage has not been detected.[28]

Cost and benefit

Any survival benefits of adjuvant treatment must be balanced against the potential adverse physical and psychological effects associated with treatment. The acute physical toxicity of adjuvant chemotherapy regimens is well known from experience in patients with node positive breast cancer.[29] The important delayed effects include permanent amenorrhoea and infertility. Data from studies of cyclophosphamide, methotrexate, and fluorouracil given as adjuvant treatment for node positive breast cancer do not show an increased risk of induction of secondary leukaemias or solid tumours.

Tamoxifen is a well tolerated treatment. Menopausal symptoms are the most commonly reported side effect, but they occur in only a minority of patients.[28] Thromboembolic events are more common in patients receiving tamoxifen. Acute toxicity does not seem to affect compliance, with equal numbers of patients stopping treatment in the tamoxifen and placebo arms in the American B-14 study. Long term treatment with tamoxifen may increase the risk of endometrial carcinoma.[30] The theoretical possibility exists that prolonged treatment with tamoxifen may alter bone or lipid metabolism, leading to accelerated osteoporosis or increased rates of cardiovascular disease, but the results of studies of this problem have been reassuring.

The psychological toxicity of treatment is less well known because of the difficulty of developing specific instruments for measuring the quality of life. Recent studies of adjuvant treatment in node positive disease have attempted to include an assessment of quality of life in the cost-benefit analysis of treatment.[31] Such assessments will be particularly important in node negative breast cancer, in which the survival benefits for patients receiving adjuvant treatment may be small.

Conclusions

Many patients with node negative breast cancer have a normal life expectancy after primary surgery. If adjuvant systemic treatment is given to all patients a large number will be treated unnecessarily. Accurate identification of this subgroup is difficult. No single feature of the primary tumour discriminates sufficiently well between high and low risk groups of patients to justify basing treatment decisions on that feature alone. Further research is needed into the ability of combinations of known prognostic factors to select such groups.

The choice of which adjuvant treatment should be offered to those patients judged suitable for it is not clear. A balance is needed between the potential benefits of a treatment and its toxicity. Chemotherapy prolongs the short term relapse free survival of some patients. It has to be determined whether this improvement will be sustained throughout a longer follow up period and whether it will truly lengthen survival. It seems most appropriate to reserve chemotherapy for patients judged to be at high risk of relapse. Tamoxifen, which has minimal toxicity, may be a more justifiable treatment for patients at lower risk.

While our understanding of the place of adjuvant treatment in the management of patients with node negative breast cancer is still incomplete there can be no justification for its widespread introduction in all patients with node negative breast cancer. Accrual of patients into well designed studies remains essential.

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