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CHANGING CONCEPTS IN THE MANAGEMENT OF BREAST CANCER*

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GENERAL CONCEPTS

Traditionally, breast cancer is a surgeon's disease, referred to, treated by and taught by surgeons. Indeed our medical SHO post on the Breast Unit at the Royal Marsden Hospital is sometimes given a low priority by potential applicants, who seem a little puzzled that it exists at all. Yet the paradox is that breast cancer is one of the great medical diseases of the late 20th century. In its metastatic form it can present with a range of clinical problems as diverse and important as, say, diabetes today or syphilis in the past; even in early breast cancer where the disease is clinically localised progress is being made almost entirely through non-surgical procedures.

Surgery emerged as the principal treatment for breast cancer in the latter half of the 19th century, following the introduction of anaesthesia, the adoption of antiseptic principles, and increasing refinement of surgical technique. Initially, some of its leading exponents had a healthy scepticism for the limitations of their skill. In a survey of his colleagues' results in 1844, Jean-Jacques Leroy found that 18 out of 1,192 patients who had not had surgery lived for more than thirty years, while only 4 out of 804 treated by surgery were alive after a similar interval; his conclusion was that operative treatment was more harmful than beneficial.[1] In 1852 James Paget came to a similar conclusion with the observation that women treated with surgery for scirrhous cancers died on average thirteen months earlier than those not given an operation.[2]

Such views were superceded by the work and writing of William Steward Halsted, Professor of Surgery at the Johns Hopkins University in the last decade of the 19th century.[3] Halsted's advocacy of the radical mastectomy did much to standardise a surgical approach to the disease that dominated modern thinking. His strategy was based on a concept that was attractive, simple to grasp, and wrong. The concept was that cancer spread centrifugally from the breast into the regional nodes which served as an initial barrier to the bloodstream. Treatment strategy was consequently surgical removal of the breast *en bloc* with regional nodes and the adjacent pectoralis muscle to prevent cancer spread and achieve cure. Subsequent generations of surgeons interpreted failure and the appearance of metastases as a flaw not in the concept itself but in the surgical technique. More and more radical procedures were devised, while developments in radiotherapy provided opportunities for evermore intensive local therapies.

Widespread acceptance that the concept itself was wrong has come very grudgingly and only within the last twenty years or so. The main source of evidence is clinical. Randomised trials with large numbers of patients and long follow-up have shown consistently, and without significant exception, that survival and the risk of metastatic recurrence in breast cancer are unrelated to the nature and intensity of local treatment.[4–9] Long term follow-up has shown that the majority of patients with so-called early breast cancer eventually develop metastatic disease irrespective of local treatment. The risk of this is greatest in patients with involved axillary nodes but these are 'an expression of a poor prognosis rather than a determinant'.[10] The only explanation for these observations is that blood-borne micrometastases must have been present at the time of initial clinical diagnosis, albeit undetectable. Indeed, modern immunocytochemical staining techniques have now demonstrated these in the bone marrow of many patients with so-called early breast cancer. In other words, for the majority of patients, breast cancer is a systemic disease at the outset and potentially curable only with effective medical therapies in addition to local treatment.

Two major changes in management have followed. The first is conservative surgery rather than mastectomy for patients with small cancers. The second is so-called adjuvant medical therapy given immediately after surgery for the great majority of patients with early clinically localised cancer.

Adjuvant medical therapy

For 25 years controversy has dominated the role of adjuvant therapy for breast cancer, but many of the initial arguments have been resolved by a recent overview analysis of all the major trials (well over 100), and these have involved around 75,000 women with breast cancer.[11] It is now established beyond doubt that both endocrine therapy (usually tamoxifen) and combination chemotherapy achieve significant survival improvement in all categories of patients with early breast cancer (at least below the age of 70); when both treatments are given together the reduction in the risk of recurrence is of the order of 40–50%.

The absolute reduction of course relates to the absolute risk; for node-negative patients with good prognosis the absolute benefit is therefore small compared with high risk node-positive patients. As a generalisation therefore, moderately low risk patients are usually treated with tamoxifen alone, and chemotherapy in addition is used for those at higher risk. Many questions remain to be answered, including the optimum duration of tamoxifen, the additional value if any of oophorectomy, and the possible role of more intensive chemotherapy schedules for patients with multiple node-involvement. Adjuvant medical therapy however, even with the limitations of currently available drugs, represents a major step forward in the management of this disease, with thousands of lives saved worldwide every year.

Primary (neoadjuvant) medical therapy: Conventional chemotherapy

A new development in breast cancer treatment with major potential implications for the future is the concept of primary (neoadjuvant) medical therapy. Here the traditional roles of management are reversed, and chemotherapy and/or endocrine therapy is given as first-line treatment before rather than after surgery. It origins lie in experience with locally advanced inoperable breast cancer where medical treatment has been increasingly used for many years prior to local radiotherapy or surgery, to try to improve local control and prolong survival.[12]

Interest in primary medical therapy developed from concern about the best management of patients with large but operable cancers for whom mastectomy rather than conservative surgery was the only conventional option because of

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tumour size or central position. The prognosis for such patients is usually poor[13] and the main rationale for this approach is therefore local control. For many women mastectomy is an unattractive option particularly if the outlook is poor anyway. Because of poor prognosis such women would subsequently be offered adjuvant medical therapy. It seemed therefore a logical development to use medical therapy first so that the primary tumour could be used as an *in vivo* measure of sensitivity to treatment, and also in the hopes that downstaging of the primary might allow mastectomy to be avoided.

This approach has shown considerable success. In our own experience in patients with large breast primaries (median diameter 6 cms) conventional combination chemotherapy with subsequent radiotherapy allows over 80% of patients who would otherwise need mastectomy to avoid this operation.[14] Other groups have reported similar findings with response rates ranging from around 70–85% using a variety of different drug combinations.[14–17] Complete clinical remissions with no residual palpable disease in the breast are uncommon however, and occur in only 15–25% of such patients.[14–17]

This latter finding is disappointing because the real success stories in cancer medicine, for example in lymphomas, testicular tumours and paediatric malignancies have evolved from novel therapies achieving high complete remission rates, and this is an essential prerequisite for a significant increase in cures. Primary chemotherapy for large breast cancer now offers an appropriate clinical model to test this hypothesis in a common epithelial cancer. The question is whether more active chemotherapy regimens can be developed to achieve a major increase in complete remission rates which might subsequently translate in significantly improved survival.

Primary medical therapy: infusional chemotherapy

With this in mind we have recently investigated a novel chemotherapy regimen based on continuous long-term infusion of 5FU delivered by ambulatory pump in combination with intermittent bolus epirubicin and cisplatin (so-called infusional ECF) as primary chemotherapy for large breast cancers. This programme is based on high activity with the same regimen in advanced gastric cancer[18] and in metastatic/locally advanced breast cancer.[19] Details of the schedule are as follows: 5-fluorouracil 200 mg/m^2 24 hourly is given by continuous intravenous infusion for up to 6 months using an ambulatory Infumed pump (Neurotechnics Ltd) and Hickman line into subclavian vein, in combination with bolus epirubicin 60 mg/m^2 and cisplatin 60 mg/m^2 IV once every 3 weeks with appropriate intravenous hydration for 6–8 courses. The schedule has proved very effective. In a pilot study of 50 patients with large operable breast cancer (median diameter 6 cms) who would otherwise require mastectomy, 49 (98%) achieved an objective response of >50% reduction in tumour size; more strikingly 33 (66%) achieved complete clinical remission of all palpable tumour. Only 3 patients (6%) still required a mastectomy. Around one third of patients had no surgery of any sort. These results suggest significantly greater clinical activity than with conventional regimens. In addition, pathological tumour cellularity was markedly reduced on repeat needle biopsy following 3 weeks of treatment in 81% of patients versus only 36% in similar patients after conventional chemotherapy ($P<0{\cdot}002$), with pathology scoring done 'blind' without knowledge of the different chemotherapy regimens. We are now carrying out a multi-centre randomised trial comparing

infusional ECF with state of the art conventional chemotherapy to answer 2 key questions: first, can we confirm that this novel infusional chemotherapy schedule does achieve significantly higher complete clinical remissions than conventional regimens, and second, will such an increased complete remission rate, if found, translate into improved long-term survival?

Primary medical therapy for small cancers

Finally, the intriguing question arises as to whether primary/neoadjuvant chemotherapy may have a survival advantage over conventional surgery followed by adjuvant therapy in patients with small breast primaries who do not require a mastectomy. There are theoretical reasons why this might be the case. Surgery and subsequent wound healing physiologically stimulate a variety of growth factors that could also promote residual tumour growth. Experimental tumour systems have indeed demonstrated stimulation of residual tumour cell growth by a serum growth factor following surgery, while prior treatment with chemotherapy suppresses this effect and prolongs survival.[20,21] Clinical trials are currently underway comparing primary/neoadjuvant chemotherapy with surgery following by adjuvant chemotherapy,[17,22,23] and preliminary results from one do indeed suggest a survival benefit.[17]

CONCLUSIONS AND THOUGHTS FOR THE FUTURE

Current standard practice in the management of early breast cancer involves initial surgery with axillary node dissection; the latter is carried out mainly as an elaborate prognostic factor with a risk of morbidity, to help in decisions about adjuvant medical therapy. We are nearing a time when similar prognostic information can be determined by immunohistochemical or immunocytological techniques using a variety of biological markers.[24] Within the next few years it is possible to envisage breast cancer being diagnosed and scored prognostically simply on the basis of fine needle aspirate cytology and immunocytochemistry. Patients at significant prognostic risk (the majority) will subsequently be treated with primary/neoadjuvant therapy using chemotherapy and/or tamoxifen with subsequent minimal residual surgery or indeed perhaps no surgery at all. Patients with a very good prognosis (the minority) will be treated with simple surgical excisions with or without the simple addition of tamoxifen.

To bring this about, today's young physicians must recognise their central importance in the initial management of this major disease of our times, and train themselves accordingly.

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THE COST EFFECTIVENESS OF CANCER CHEMOTHERAPY: A CLINICIAN'S VIEW★

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The purchaser/provider scenario is now integral to current United Kingdom National Health Service practice. Therapeutic advances have improved the treatment options available, but these together with demographic changes and the rise of expectations of a more health conscious public, are placing increasing demands on limited resources. In Oncology, as indeed in many other specialities, in drawing up contracts purchasers are still uncertain as to what they should demand to achieve the best quality and most cost-effective care for their patients. The onus is on expert providers to advise purchasers on up-to-date practice in sensible terms.

VALUE ANALYSIS (ECONOMIC EVALUATION)

Methods of evaluating treatment options include. (1) Cost minimisation, which examines and compares the total costs of using different treatments giving identical outcomes, (2) Cost effectiveness, which relates the cost of therapies to their outcomes, where outcome is assessed in terms of a single health effect, (3) Cost benefit analysis, which compares total benefits of using a given treatment with all the associated costs, with the measurement in financial terms, and (4) Cost utility, which relates the cost of different therapies to the amount of 'well being' produced. One variation of cost-utility assessment is the Quality Adjusted Life Year (QALY), but this has not found universal favour amongst clinicians and managers.

There is an acknowledged lack of outcome measures in Oncology, particularly in terms of palliative therapies where survival data are not particularly relevant. 'Concrete' markers of quality are required with quality of life (QOL) measurement the ideal. Unfortunately, as the considerable array of tests available for the assessment of QOL may indicate, this is not an easy task and such measures are not easily comprehended by health care managers, although some tests do seem to be of value as true reflectors of patients' experience. However, it is generally agreed that objective tumour response (complete, partial or none) as defined by the standard Union Internationale Contre Cancer (UICC) criteria does correlate with quality as far as the patient's perception of benefit is concerned.

CHEMOTHERAPY

The total cost of drug management in cancer therapy must include factors other than the agents used. These costs will also include time and other materials (including nursing/medical resources), and must take into account supporting

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