Chemotherapy for Breast Cancer

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Abstract **- Breast cancer represents a major health problem, with more than a million new cases and 370,000 deaths worldwide yearly. Breast cancer remains the most prevalent form of cancer among women. The use of cytotoxic chemotherapy in both advanced and early-stage breast carcinoma has made significant progress in the last 10 years with several landmark studies identifying clear survival benefits for newer therapies. Cytotoxic combination regimens developed in the 1970s were shown to produce higher response rates and longer durations of response and survival than single agent therapy. These regimens became the standard of care for the management of metastatic hormone- refectory breast cancer and more recently for primary breast carcinoma, randomized trials also have demonstrated that anthracycline containing combination were more effective than combination without anthracyclins. The improvement in the understanding of the molecular biological basis of breast cancer provides possible targets for novel therapies. This review will focus on the evidence j use of chemotherapy.**

Index Terms **- Breast cancer, cytotoxic chemotherapy, metastatic breast carcinoma, anthracycline, chemotherapy.**

INTRODUCTION

Breast cancer represents a major health problem, with more than a million new cases and 370,000 deaths worldwide yearly. According to the American Cancer Society, an estimated 211,000 women will be diagnosed with breast cancer, approximately 40,000 women will die of the disease in the USA in 2005, and breast cancer remains the most prevalent form of cancer among women. In the past 10 years, in spite of an increasing incidence, breast cancer mortality has been declining in most developed countries. The use of systemic therapy in early breast cancer is undoubtedly a major reason for that. What we find striking in breast cancer is that although the risk of distant recurrence is greatest during the first decade, it may still be significant during the second decade post diagnosis. The main aim of systemic adjuvant treatment is to control any micrometastatic disease, reduce the recurrence rate, and improve the long-term overall survival. Since most of the improvement in 15-year breast cancer mortality produced by adjuvant chemotherapy and hormonal therapy and by adjuvant radiotherapy. Occurs after the first 5 years, there may be a delay of a decade or so between any widespread changes in practice and the main effects that these will eventually have on national breast cancer mortalityrates. Thus, earlier diagnosis, wider use of adjuvant treatments, or both, during the 1980s contributed significantly the sudden decreases of 25-30% noted in the USA and UK breast cancer mortality rates. Further moderate improvements during the 1990s involving better local disease control (partly because of more careful and more extensive screening) and better use of systemic treatments both for early and for advanced disease should in total help these decreases in national mortality rates to continue throughout the present decade. Despite improvements with better understanding of the use of adjuvant therapies for early-stage breast cancer, the treatment of metastatic disease remains a major challenge. The use of anthracyclines and taxanes in the adjuvant setting has led to an increasing number of women presenting with metastatic disease having already been exposed

to these agents adding to the complexities of their management. Despite being incurable, metastatic breast cancer (MBC) often remains chemosensitive such that symptom control and prolongation of survival can be achieved.

However, response duration remains disappointingly short-and long-term survival remains uncommon. Breast cancer remains a classic model where chemotherapy treatments have been tested in advanced metastatic settings and having shown efficacy with tolerable toxicity have marched into the adjuvant setting. New endocrine therapies, such as pure estrogen receptor antagonists, have already entered the clinic. Furthermore, the development of trastuzumab, a humanized monoclonal antibody against HER-2/neu (HER2-neuThis is a transmembrane receptor similar to epidermal growth factor receptor that is overexpressed in 25 per cent of breast tumours58 and associated with poor outcome59.Overexpression of HER2-neu is associated with increased sensitivity to anthracycline regimens in the adjuvant setting. Present data on HER2-neu status and response to neoadjuvant anthracycline chemotherapy are conflicting60.Studies relating HER2-neu and response to taxanes as adjuvant therapy have been reviewed recently61; the relationship between HER2-neu overexpression and response to taxanes is positive but 1984;2:1281– 8.31. Tannock IF, Boyd NF, DeBoer G, Erlichman C, Fine S, La-rosque G, et al. A randomized trial of two dose levels of cyclophosphamide, methotrexate, and fluorouracil chemotherapy for patients with metastatic breast cancer. J Clinocol 1988; 6:1377– 87.32. Bissery M-C, Nohynek G, Sanderink G-J, Lavelle F. Docetaxel (taxotere): A review of preclinical and clinical experience. Part I: preclinical experience. Anticancer Drugs 1995; 6:339 –55. Tentative) provides the first example of a targeted biologic therapy for breast cancer being extensively used in the advanced setting; now, with preliminary data indicating unprecedented activity in early stage disease, it has the potential to make a major impact on breast cancer mortality. Despite these developments, resistance to therapy remains a key limitation in the management of advanced breast cancer. Options and understanding of how to use cytotoxic chemotherapy in both advanced and early-stage breast cancer have made substantial progress in the past 10 years, with numerous landmark studies identifying clear survival benefits for newer approaches. Despite this research, the optimal approach for any one individual patient cannot be determined from a literature review or decision-making algorithm alone. Treatment choices are still predominantly based on practice determined by individual or collective experience and the historic development of treatment within a locality. In many situations, treatment decisions cannot be divorced from economic consideration. Blanket application of international, national or local guidelines is usually impractical or inappropriate and careful consideration of the detailed circumstances of each patient is needed to make optimal use of available options.

ADJUVANT THERAPY

Adjuvant therapy is treatment given in addition to your breast surgery. its used to kill any cancer cells that may be left in your breast. Early breast cancer disease is detected only in the breast, With or without the involvement of locoregional lymph nodes, amenable to complete surgical removal. However, undetected deposits of disease may remain either locally or at distant sites and, if untreated, could eventually develop into a life-threatening clinical recurrence. The main aim of systemic adjuvant treatment is to control any probable micrometa-static disease, thereby reducing the recurrence rate and improving long-term survival Over the past few decades, many randomised trials have been undertaken of various treatments for early breast cancer, but the duration of follow-up varies greatly between different trials and between different patients in the same trial. Hence, meta-analyses of the effects of such treatments on long-term outcome in various types of patient can deliver important insights into the value of different treatment concepts. With continued improvements in local disease control (partly because of more careful and more extensive screening) and better use of systemic treatments both for early and for advanced disease a continued decrease in national mortality rates is anticipated.

ROLE OF ANTHRACYCLINES

Anthracyclines possess significant activity as single agent in first-line therapy of patients with advanced breast cancer with responses rates of 30–40%. Meta-analysis of 30 trials has shown that polychemotherapy regimens containing anthracycline were associated

with superior response rates, but without a significant survival benefit compared with regimens without anthracycline, and with increased gastrointestinal toxicity, cardiotoxicity and alopeci. This meta-analysis is, however, limited by its use of published data only, as well as the heterogeneity of patients and their previous treatments. Furthermore, analysis suggested that the addition of an anthracycline to a chemotherapeutic regimen (as opposed to it replacing another drug or being used alone) did, in fact, improve OS. Pagylated liposomal doxorubicin may result in improved pharmacokinetics and preferential accumulation of drug in the tumor. Such tumor selectivity is thought to be mediated by increased permeability of tumor vasculature and impaired lymphatic drainage allowing accumulation of macromolecules, the so-called enhanced permeability and retention effect.

ROLE OF TAXANES

Taxanes have emerged as critically important drugs in the treatment of breast cancer. Five trials of adjuvant chemotherapy compared a taxane-containing regimen with a non-taxane containing regimen. Involving more than 9,000 women with 2,512 relapses and 1,591 deaths the treatment approaches that were investigated were heterogeneous. A systematic review of randomised

trials of adjuvant or neoadjuvant systemic therapy recently published identified ten reported trials comparing a taxane-containing group with a non-taxane-containing control group in women with early 1984; 2:1281– 8. 31. Tannock IF, Boyd NF, DeBoer G, Erlichman C, Fine S, La-rocque G, et al. A randomized trial of two dose levels of cyclophosphamide, methotrexate, and fluorouracil chemotherapy for patients with metastatic breast cancer. J Clinocol 1988; 6:1377– 87.32. Bissery M-C, Nohynek G, Sanderink G-J, Lavelle F. Do-citadel (taxotere): A review of preclinical and clinical exp-. Part I: preclinical experience. Anticancer Drugs 1995; 6:339 –55. Breast cancer. Four of five neoadjuvant trials showed higher rates of complete response with taxanes, although difference was not significant. All five adjuvant trials showed improvements in DFS with taxanes, and these improvements were significant in three trials and were independent of oestrogen-receptor status. Two trials showed a significant improvement in overall survival. These results are used to support the use of adjuvant taxanes in women with early node positive breast cancer. Longer follow-up of these trials and results from ongoing trials are needed to clarify the best use of taxanes in early breast cancer. The strongest evidence is for the addition of four cycles of paclitaxel to four cycles of doxorubicin and cyclophosphamide, or for the substitution of six cycles of FAC with six cycles of docetaxel, doxorubicin, and cyclophosphamide. This effect is independent of hormone-receptor status, and the evidence does not support restricting the use of taxanes to women with hormone-receptor negative tumours. There is also evidence suggesting that docetaxel and cyclophosphamide is an acceptable alternative to doxorubicin and cyclophosphamide, although long-term data on this regimen is lacking. Roche et al presented the data on the 6 cycles of FEC 100 (Arm A) as compared to 3 -cycles of FEC 100 followed by 3 cycles of Docetaxel (Ar B) for node positive breast cancer patients. Between June 1997 and March 2000, 1,999 patients were recruited in 83French and Belgian centres. More febrile neutropenia and nail disorders were observed in Arm B and a more decreases and subnormal LVEF at the end of chemotherapy in Arm A Five cases of leukaemia (3 Arm A; 2 Arm B) were observed. No toxic deaths have been reported. The substitution of 3 cycles of docetaxel for 3 cycles of FEC 100 following 3 cycles of FEC 100 significantly improved DFS and overall survival.1984;2:1281– 8.31. Tannock IF, Boyd NF, DeBoer G, Erlichman C, Fine S, La-rocque G, et al. A randomized trial of two dose levels of cyclophosphamide, methotrexate, and fluorouracil chemotherapy for patients with metastatic breast cancer. J ClinOncol 1988; 6:1377– 87.32. Bissery M-C, Nohynek G, Sanderink G-J, Lavelle F. Docetaxel (taxotere): A review of preclinical and clinical experience. Part I: preclinical experience. Anticancer Drugs 1995; 6:339 –55. There was a 17% reduction in the risk of relapse (HR 0.83, range 0.69-0.99) with a P-value of 0.041. Five-year overall survival was 90.7% for the sequential arm as compared to 86.7% for 6 cycles of FEC 100 arm (P=0.017). There was thus a 23% reduction in the risk of death (HR 0.77, range 0.59-1.00) with a P-value of 0.05 (Roché H, et al, San Antonio Breast Cancer Symposium 2004). There are 15 unreported trials including more than 19,000 women addressing similar and related

questions (Riou JF, et al, Proc AACR 385: 1994). Longer follow-up of all trials is needed to clarify the role of taxanes in the treatment of early breast cancer. Based on indirect comparisons as well as the results of the recent randomised trial conducted in patients with MBC, docetaxel appears to be the more active taxanes. In addition to its longer half-life, docetaxel also has a more rapid cellular uptake and longer intracellular retention than paclitaxel. Because of its pharmacokinetics, the efficacy of paclitaxel is schedule dependent. In general, trends of superior response rates have been associated with higher doses and prolonged infusions times, but no regimen of paclitaxel has been shown to be statistically superior to any other in MBC. Docetaxel is highly active when given as a short, intermittent infusion. Dose-dense paclitaxel-based therapy, in which chemotherapy cycles are administered every 2 weeks has produced impressive results in the adjuvant setting. It remains to be determined if this approach is superior to conventional docetaxel-based therapy in this setting or if a dose-dense docetaxel-based regimen will be similarly effective. At the current time, clinicians should choose a taxanes-based regimen for their patients with breast cancer based on consideration of the pharmacokinetics, clinical activity, toxicity and dosing schedule that best meets the patients' needs. Results from ongoing and recently completed trials will no doubt improve outcome and quality of life for patients with early-stage breast cancer. Future trials should shed light on their ideal amalgamation with existing and promising treatments.

CONCLUSION

Increasing evidence suggests we need to apply different approaches to understanding the role of chemotherapy in ER-positive and ER-negative disease. ER-negative disease tends to have a disproportionate impact on early events in trials of adjuvant chemotherapy partly as a result of being a generally more aggressive phenotype and partly because the impact of adjuvant endocrine therapy suppresses early relapses in ER-positive disease. Recent research has allowed us to refine breast cancers further into prognostic groups based on gene expression profile. It is anticipated that we will be able to utilise expression profiles to guide adjuvant chemotherapy decisions in patients where the indication for chemotherapy on conventional grounds is borderline, and to avoid unnecessary chemotherapy in patients with adverse conventional features who carry a favourable gene expression signature since benefit in these patients is predicted to be low. Clinical trials to prove the value of this approach are currently being designed. Assuming these approaches are successful we will need to develop our ability to roll out the findings into routine practice. While there remains much potential for further refinement of conventional cytotoxic agents the largest leaps forward are likely to come from incorporation of targeted therapies. Trasuzumab has produced quite startling results in the adjuvant context and whilst unrealistic to expect many more results of this magnitude new agents such as the VEGF antibody bevacizumab are now showing promising results in advanced disease in breast cancer and are being tested in the adjuvant setting in high-risk patient groups. The future for breast cancer therapy is brimming with promise but it is important to be prepared for disappointment and remember that no number of mice cured in model experiments can guarantee a successful human therapy. Breast cancer therapy development will however probably remain true to form of the last 30 years with drugs demonstrating clear superiority in controlling advanced disease proving to be even more valuable in treatment of early disease. The abundance of molecular therapies that are emerging from better understanding of cancer biology provides an optimistic climate for the future of breast cancer.

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