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Meeting Report: Long-term Antihormonal Therapy for Breast Cancer

Alberto Costa and V. Craig Jordan

TAMOXIFEN IS a non-steroidal anti-oestrogen that is available to treat selected patients with all stages of breast cancer [1]. Early laboratory studies demonstrated [2] that long treatment schedules might be an appropriate strategy to use as adjuvant therapy following mastectomy in node-positive and node-negative disease. Clinical trials organisations have focussed on long-term tamoxifen therapy which has become an important part of the therapeutic armamentarium to prevent the recurrence of breast cancer following mastectomy.

During a 3-day international meeting (Chairman, V.C. Jordan) in Orlando, Florida (29 June–2 July 1991), the University of Wisconsin Comprehensive Cancer Center (Director, P.P. Carbone) hosted a review of progress to evaluate the efficacy and safety of tamoxifen therapy. The goal of the conference was also to discuss possible mechanisms of drug resistance to tamoxifen that have been identified in the laboratory and to consider the prospects for new breast cancer treatment strategies.

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EFFICACY OF TAMOXIFEN

Paul Carbone noted that the concept of extended (5+ years) adjuvant tamoxifen therapy was piloted at Wisconsin as a direct result of the early laboratory data [2]. The studies that demonstrated the effectiveness of long-term tamoxifen therapy in preventing rat mammary carcinogenesis were first presented at a meeting in Cambridge, UK in 1977. The laboratory and clinical results [3] provided the information to establish ECOG trials of chemotherapy and different durations of tamoxifen therapy (1, 5 or indefinite years) in both premenopausal and postmenopausal patients. At present early analysis of ECOG trials demonstrate an increase in disease-free survival for patients receiving at least 5 years tamoxifen (10 mg twice daily) (D.C. Tormey, Madison). Oestrogen receptor (ER) positive disease is more likely to respond to tamoxifen in ECOG studies and in the Stockholm trial of adjuvant tamoxifen (2 or 5 years) the presence of the ER was a prerequisite for a response to tamoxifen (L. Rutqvist, Stockholm). In contrast, tamoxifen was noted to be efficacious in ER-poor patients from both CRC (M. Baum,

London) and Scottish (H. Stewart, Edinburgh) trials in premenopausal and postmenopausal disease.

The incidence of contralateral breast cancer did, however, provide some interesting insights into the disease that might have implications for future prevention studies in normal women. There is a statistically significant reduction of second breast cancers in all studies (CRC, NATO, Scottish, Swedish, NSABP). However the CRC trial of two years of adjuvant tamoxifen only shows a decrease in contralateral primary breast cancers in postmenopausal patients (M. Baum, London). In contrast, the NSABP study (B14) noted decreases in both premenopausal and postmenopausal patients. This could be explained because the duration of tamoxifen therapy was longer (> 5 years) in the NSABP study. Interestingly enough, in the Stockholm study second primaries were more likely to be ER-negative. 53% were ER positive in the tamoxifen-treated group vs. 88% in controls (L. Rutqvist, Stockholm).

SAFETY OF LONG-TERM TAMOXIFEN

All clinical trials note that tamoxifen is a well-tolerated drug and few patients withdraw from studies because of serious side-effects. The pharmacology of long-term (up to 10 years) adjuvant tamoxifen therapy has been evaluated. Stable serum levels of tamoxifen and its metabolites have been noted and there has been no metabolic tolerance or the appearance of unusual or overtly oestrogenic metabolites (V.C. Jordan, Madison).

A principal concern during the past decade has been the possibility that tamoxifen, an anti-oestrogen, could increase the incidence of coronary heart disease or osteoporosis. The Wisconsin Tamoxifen Study has gone some way to address these concerns. 140 postmenopausal node-negative breast cancer patients were randomised to receive placebo or tamoxifen (10 mg twice daily) for 2 years. A significant and sustained maintenance of sacral spine bone density was observed compared to decreases observed in the placebo arm (R.R. Love, Madison). Similarly significant decreases in circulating cholesterol, primarily LDL cholesterol, have been observed during tamoxifen therapy. This could translate into additional benefits for the postmenopausal patient. Indeed, a 10-year analysis of the Scottish trial (tamoxifen 10 mg twice daily for 5 years vs. tamoxifen at recurrence in the control arm) has noted a lower incidence of myocardial infarction in the arm receiving adjuvant tamoxifen (H. Stewart, Edinburgh).

Tamoxifen exhibits a balance of oestrogenic and anti-oestrogenic actions that could be beneficial during long-term tamoxifen therapy. Nevertheless, concerns about the potential of tamoxifen to promote carcinogenesis in the laboratory and clinic were reviewed. Tamoxifen causes a dose-related increase in rat liver cancers. Several investigators have noted that long-term treatment of rats with daily doses of tamoxifen of greater than 10 mg/kg results in hepatocarcinogenesis. However, studies at the McArdle Laboratory (Y.P. Dragon and H.C. Pitol, Madison) have demonstrated that tamoxifen is a promoter of carcinogenesis rather than a carcinogen. Tamoxifen acts as a weak oestrogen, i.e. natural and synthetic oestrogens are much more efficient and potent at promoting liver cancer. Indeed the doses of tamoxifen used to determine hepatocarcinogenesis are far higher than would be expected during human exposure or are required to prevent mammary carcinogenesis in animal models (C. Maltoni, Bologna).

Oestrogen therapy is also known to promote endometrial carcinogenesis. In an update of the Stockholm trial of up to 5 years of adjuvant tamoxifen (20 mg twice daily), 18 endometrial tumours have been noted compared to 2 in controls (L. Rutqvist, Stockholm). There are approximately 1000 patients in control or tamoxifen-treated arms. Although other clinical trial organisations have not noticed similar significant increases in endometrial carcinoma another Scandinavian study of 30 mg tamoxifen daily has noted an increase. The known survival benefit documented for patients receiving adjuvant tamoxifen makes tamoxifen the endocrine treatment of choice for breast cancer but a patient should not be denied tamoxifen because of the potential to promote endometrial carcinoma. However, physicians should regard endometrial carcinoma a possible complicating factor during extended tamoxifen therapy. All cases of abnormal vaginal bleeding should be followed up with gynaecological investigation (V.C. Jordan, Madison).

Drug resistance

Combinations of tamoxifen and chemotherapy are commonplace in the adjuvant treatment of breast cancer. However the question can be asked, "is this an optimal treatment strategy?" Careful laboratory studies have demonstrated that tamoxifen can antagonise the antitumour actions of melphalan and cyclophosphamide whereas combinations of doxorubicin and tamoxifen may be synergistic. Tamoxifen may prevent doxorubicin efflux from cells by blocking the gp170 membrane pump (C.K. Osborne, San Antonio). A current intergroup study is addressing these concerns by comparing tamoxifen versus tamoxifen plus cyclophosphamide/doxorubicin/5-fluorouracil (CAF) versus CAF followed by long-term tamoxifen therapy.

Another issue is the development of tamoxifen-stimulated growth during continuous tamoxifen therapy. Although the phenomenon is poorly defined in the clinic, the process has been described independently by two laboratories (C.K. Osborne, San Antonio and V.C. Jordan, Madison). The San Antonio group has demonstrated that athymic mice inoculated with MCF-7 breast cancer cells will only produce palpable tumours if the animals are treated with oestrogen. Tamoxifen inhibits oestrogen-stimulated growth but eventually, after months of tamoxifen treatment, tumours grow during anti-oestrogen therapy. The tumours are ER-positive and changes in the ratio of certain geometric isomers of metabolites of tamoxifen have been noted that could be responsible for tamoxifen-stimulated growth or at least be markers of tamoxifen resistance (C.K. Osborne, San Antonio).

In contrast, the Wisconsin group noted that analogues of tamoxifen that cannot change to oestrogenic isomers of tamoxifen are still promoters of rat hepatocarcinogenesis (Y. Dragan, Madison) and will support the growth of tamoxifen-stimulated breast tumours in athymic mice (D. Wolf, Madison). Clearly this is an important area for further investigation.

FUTURE CONSIDERATIONS

The rigorous evaluation of long-term adjuvant therapy for breast cancer during the past decade has not only placed a valuable agent in the hands of the clinician but has also provided the clinical research community with an agent to test as a preventive in normal women at risk for breast cancer. It is hoped that the cardiovascular and bone effects of tamoxifen will in general provide additional beneficial effect for women's health.

Three major studies are about to start. In the UK, high-risk women will be treated for 5 years with 20 mg tamoxifen (M. Baum, T. Powles, London). In Italy, hysterectomised high-risk women aged 45–65 years will be treated for 5 years with low-dose tamoxifen (10 mg daily) (U. Veronesi, Milan). In the

USA the FDA has approved a trial to be conducted by the NCI/NSABP for high-risk women over the age of 35 years or all women over the age of 60 years. Women will be randomised to receive 5 years tamoxifen (20 mg daily) or placebo (B. Fisher, Pittsburgh).

Improvements in the endocrine therapy of advanced disease are also being attempted by comparing tamoxifen plus a luteinising hormone-releasing hormone (LHRH) agonist (goserelin) versus goserelin alone. Preliminary results suggest an improvement in the duration and survival of responsive patients receiving the combination. Recruitment of 350 patients to a large trial is complete and an analysis will be made in late 1991 (R. Blamey, Nottingham).

Similarly a new drug, ICI 182,780, is about to be evaluated to treat patients who fail long-term adjuvant tamoxifen therapy. The drug is a pure anti-oestrogen in laboratory tests and has now successfully passed the initial toxicology evaluation (A. Wakeling, Macclesfield). The mechanism of action of pure anti-oestrogens seems to be to prevent receptor dimerisation that is required for interaction at the DNA to activate oestrogen-specific genes (M.G. Parker, London). The pure anti-oestrogen (ICI 164,384, a compound related to ICI 182,780) inhibits the growth of tamoxifen stimulated tumours in the laboratory so this new class of drug can potentially be used as a second-line endocrine therapy after tamoxifen (V.C. Jordan, Madison). Clinical evaluation has started in the UK.

Finally, novel new strategic approaches to treat breast cancer were considered. Most disease is hormone-independent so progress to control cell replication would have an enormous impact on patient survival. Two approaches were developed by Marc Lippman (Washington). Firstly, hormone independent cells can overexpress *erb* B2 and the Georgetown group has identified the ligand that activates the membrane receptor. Novel *erb* B2 blocking drugs could become valuable new theraputic agents. Secondly, breast cancer cells secrete fibroblast growth factor-like substances that are necessary to allow tumour growth and homeostasis. Specific polysulphated molecules will prevent tumorigenesis in the laboratory and some have now entered clinical trial.

In a closing overview the successful transfection of the ER gene into hormone-independent breast cancer cells was described (V.C. Jordan, Madison). The growth of these stably transfected cell lines is inhibited by oestrogen; however pure anti-oestrogens have no effect on growth but block the inhibitory effect of oestrogen (S.Y. Jiang and V.C. Jordan, Madison). These novel studies may provide exciting therapeutic opportunities for the future. If a hormone refractory breast cancer cell can be "reinfected" with the ER gene through a targeted gene therapy then a weakly oestrogenic agent like tamoxifen could continue to control the growth of the disease. Indeed, the concept could be taken further. Perhaps any cancer could be infected with ER to provide a therapeutic advantage for the patient. It is possible that this is the dawn of a new era and the work of the molecular biologist can be focussed and targeted towards receptor pharmacology as a novel gene therapy.

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Multidrug Resistance from the Clinical Point of View

Coenraad K. van Kalken, Herbert M. Pinedo and Giuseppe Giaccone

INTRODUCTION

CHEMOTHERAPY is a curative treatment modality for several types of tumours even in advanced stages, like testicular cancer, a number of cancers of childhood and some haematological malignancies [1]. Other tumours such as ovarian cancer, acute myeloid leukaemia (AML), small cell lung cancer and advanced breast cancer, achieve high response rates and prolongation of survival by combination chemotherapy, but unfortunately they frequently relapse after an initial response and are then broadly resistant to drugs. Furthermore, common malignancies, like non-small cell lung cancer and colon cancer, are poorly responsive to chemotherapy from their diagnosis.

Causes of failure of chemotherapy are multifactorial and range from physical inability of the drugs to reach the critical cellular target (i.e. poor absorption, unfavourable pharmacokinetics and distribution, poor tumour vascularisation, low pH, etc.) to diverse cellular mechanisms of resistance. Drug sensitivity is intimately related to tumour growth kinetics and tumour volume; however, recently more emphasis has been given to the investigation of cellular mechanisms of resistance to drugs.

The hypothesis of spontaneous mutations as cause of drug resistance development, proposed by Goldie and Coldman in

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