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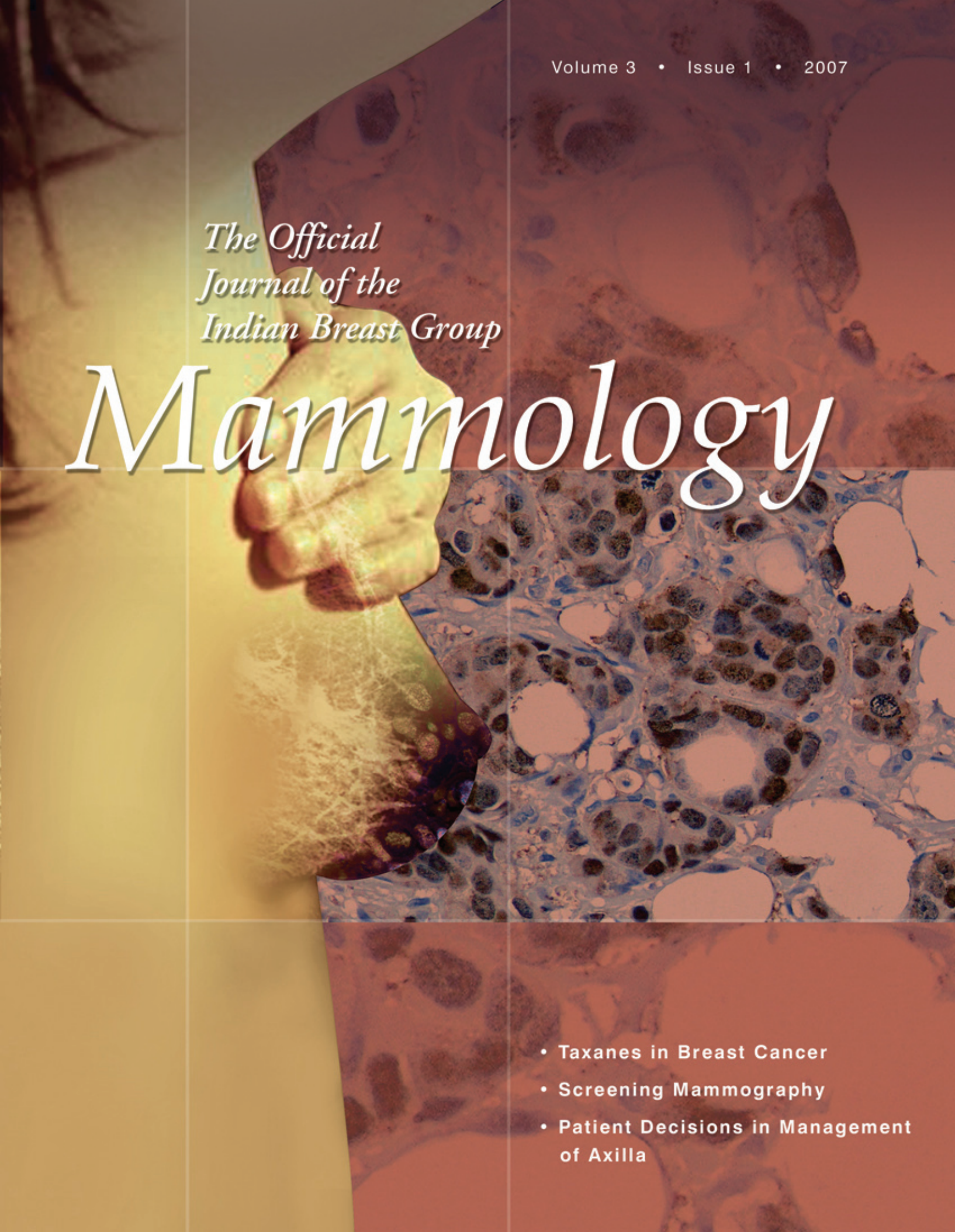

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Mammology

- Taxanes in Breast Cancer
- Screening Mammography
- Patient Decisions in Management of Axilla

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Mammology

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Cover

Electron photomicrograph of estrogen receptor staining in breast tissue.

From the Editor's Desk

Last issue of *Mammology* covered the whole spectrum of breast cancer research; from molecular methods to clinical research relevant in Indian context. In this issue we will be focusing more on day-to-day clinical questions.

Although screening for breast cancer has become a standard practice in western world, it is not yet widely practiced in India. It is very important to understand the available evidence, assess its applicability in our context instead of blindly following the western world. Additionally, current scenario also offers hope from a global research perspective; we can answer certain questions that western world cannot since they have missed the opportunity of answering questions like whether clinical breast examination decreases breast cancer mortality or not. Sushma Agrawal et al review the current evidence for and against breast cancer screening and applicability of such evidence to Indian women.

Adjuvant systemic therapy for breast cancer has undergone major changes in past few years with arrival of trastuzumab and aromatase inhibitors. This, however, has not decreased the importance of adjuvant systemic chemotherapy, which majority of patients in this part of world have to undergo to improve their chances of survival. Taxanes have emerged as important chemotherapeutic agents in breast cancer treatment. Jean-Marc Nabholtz has conducted adjuvant therapy trials on both sides of Atlantic, many of which evaluated role of taxanes in breast cancer treatment. He shares his insight in his very comprehensive review of the subject.

Importance of ER status in treatment decisions cannot be overemphasised, but many clinicians are unaware of the impact specimen processing can have on ER estimation. Non-uniform specimen processing can give rise to highly variable results, which has been one of the main reasons for low ER positivity reported from Indian subcontinent. A clinician can very well understand the negative impact of an ER positive patient being falsely called ER negative and being denied effective endocrine therapy due to suboptimal ER estimation. In a simple but elegant study, Tanuja Shet and colleagues demonstrate how only changing the fixative, merely a step in specimen processing for many of us, can affect ER estimation.

In this era of strong advocacy of sentinel node biopsy and plenty of information available through Internet, patient participation in axillary treatment decisions has significantly increased. It is imperative for a clinician to know and understand what an informed patient desires and wants to know more. Hazel Thornton has not only been awarded a doctorate for being the most informed patient but also has co-authored a widely acclaimed book titled "Testing Treatments: Better research for better healthcare". She gives us an informed patient perspective of management of axilla in breast cancer.

Anusheel Munshi reviews a randomized trial of CMF chemotherapy versus ovarian ablation by radiation in the Journal Watch section while Vani Parmar brings us the latest happenings from San Antonio symposium.

Though clinical management is the focus of this issue, we do not want to lose the opportunity to sensitise our readers to basic and translational research. Sen Pathak from MD Anderson gives us insights about how research involving cancer cell lines, which often is an important first step, is conducted and how contamination in cell lines can throw us off the track. His review is lucidly peppered with historical snippets and his own interesting personal experiences. Rakesh Kumar from the same institute takes us further on the research track to bench-to-bedside medicine, sharing his perspective on partnership between basic and clinical research and his tips to make it successful. He aptly encourages clinicians to play their part and also get conversant with basic research, which is conducted in English, certainly not in Roman or Greek, if only we were to make an attempt.

Dr. Mangesh Thorat **25th June 2007**

Taxanes in Breast Cancer

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Abstract

Breast cancer is one of the most frequent cancers for women in the world. Systemic chemotherapy has improved the outcome of patients treated for invasive breast cancer, in particular in adjuvant setting. Among new chemotherapeutic agents developed in the 1990s, the taxanes have emerged as the most powerful compounds since anthracycline regimens. The two taxanes (paclitaxel and docetaxel) share some characteristics, while having some significant differences both in terms of preclinical and pharmacokinetic profiles with, as a consequence, some remarkable clinical differences. In clinical practice, the taxanes are now considered standard therapy in metastatic breast cancer. Their role as monochemotherapy or in combination with anthracyclines in advanced breast cancer has suggested their potential therapeutic impact in the treatment of patients with early breast cancer. Available results in adjuvant and neoadjuvant setting show that taxanes, used in combination with other chemotherapeutic agents or trastuzumab, or in sequential therapy, possess the capability to induce significant improvements, particularly in terms of survival, confirming the positive impact of taxanes on the natural history of breast cancer.

Introduction

Among the cytotoxic agents developed during the last decade for the treatment of breast cancer, the taxanes have emerged as the most powerful compounds. Following the traditional model of drug development, both paclitaxel and docetaxel were extensively studied initially as single agents in patients with metastatic breast cancer (MBC) (Table 1). Recognized early as major drugs, they were then combined with other chemotherapeutic agents, being added to the previous most effective agents (anthracyclines, in particular) in second-line and first-line MBC therapy. Subsequently, they were logically investigated in adjuvant and neoadjuvant programs in order to establish their role in early breast cancer.

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Taxanes in metastatic breast cancer

Taxane monochemotherapy in advanced breast cancer

Both paclitaxel and docetaxel have substantial activity as single agents in the treatment of metastatic breast cancer.

Paclitaxel has shown significant anti-neoplastic activity against a number of solid tumors.[1] Originally, phase I and II trials were conducted using a variety of doses and infusion schedules confirming a good single-agent activity against MBC, but generated some confusion as to its most effective administration. Large randomized studies suggested that a dose of 175 mg/m^2 (delivered over three hours every three weeks) is both efficacious and tolerable.[2] However, dose escalation and the use of prolonged infusion schedules (24–96 hours) yielded better outcome.[3,4] Though still debated by some authors, the question of the optimal schedule and dose for paclitaxel has been largely answered.[3] In fact, schedule and dose appear to play a combined role in the definition of the efficacy toxicity ratio. Paclitaxel was initially shown to be very active when given at high doses (250

Table 1. Early clinical development differences between docetaxel and paclitaxel

Property	Docetaxel	Paclitaxel
Beta tubulin affinity	1.9	1
Plasma clearance	Linear	Non-linear
Interaction with Anthracyclines	No cardiotoxic effects Effects not sequence dependent	Enhanced cardiac toxicity Effects sequence dependent
Hypersensitivity	None	Attributed to Cremophor EL
Fluid retention	Avoidable with prophylactic treatment	None
Schedule and dose	Two possible regimens • 3 weekly 1 hour infusion 100 mg/m² • Weekly regimen 1 hour infusion 35–40 mg/m²	Different possible schedules and doses • 3 weekly 3 hours infusion 175–225 mg/m² • 3 weekly 24 hours infusion 135–250 mg/m² • Weekly regimen 1 hour infusion 80–100 mg/m²

mg/m^2) over long schedules (24 hour): response rates were, in this context, consistently in the 50% range. But, this was obtained with a high toxicity (neutropenia, fatigue, etc.) and poor practicality. Although lower doses (175–200 mg/m^2) given over short infusion (three hours) were more feasible, with easy outpatient administration, they consistently showed less efficacy (response rates in the 25–30% range) in large scale randomized trials. More recently, weekly infusions have displayed some significant advantages both in terms of efficacy and safety profile, and some authors consider weekly as the optimal schedule at a dose of 80–90 mg/m^2 for paclitaxel administration.[4]

Single agent paclitaxel was compared to doxorubicin monotherapy in two phase III trials. In one study, paclitaxel (200 mg/m^2 delivered over three hours every three weeks) was shown to be significantly inferior to doxorubicin (75 mg/m^2),[5] while first line paclitaxel (175 mg/m^2 given over 24 hours) was comparable to doxorubicin (60 mg/m^2).[6]

Docetaxel also has emerged as one of the most active drugs against advanced breast cancer. For docetaxel, the situation was more straightforward and there has been no particular controversy surrounding the recommended schedule and dose, which was clearly established as 100 mg/m^2, one hour infusion every three weeks and subsequently used for monochemotherapy phase III trials in advanced disease. In these studies, docetaxel compared favorably to doxorubicin (75 mg/m^2)[7] and showed a significant superiority to various salvage regimens after prior exposure to anthracyclines[8–10] with the potential to improve survival.[8] As for paclitaxel, data were reported on the use of weekly docetaxel and have confirmed the same trend with a threshold of toxicity around 40 mg/m²/week.

These results positioned these agents as compounds to further develop in advanced and adjuvant therapy of breast cancer.

Taxane combinations in advanced breast cancer

The next phase in the development of the taxanes was to combine them with other active agents. Most pivotal trials have initially focused on taxane-anthracyclines combinations for the following reasons:

1. Greatest activity as monotherapy.
2. Incomplete clinical cross-resistance.
3. No overlap of side effect profiles (with the exception of myelosuppression).

Table 2. Early clinical development differences between docetaxel and paclitaxel

Author	Regimens*	N	ORR (%)	TTP (months)	Survival (months)
Sledge et al, 2003 [6]	T 175 A 60 AT: A50 + P150	739	33 34 46 p = NS	5.9 6.2 8.0 p < 0.05	22.0 20.1 22.4 p = NS
Jassem et al, 2001 [14]	AT: A50 + T220 FAC: F500 + A50 + C500	267	68 55 p = 0.03	8.3 6.2 p = 0.03	23.3 18.3 p = 0.01
Biganzoli et al, 2002 [15]	AT: A60 + T175 AC: A60 + C600	275	58 54 p = NS	NA	NA
Luck et al, 2000 [16]	ET: E60 + T175 EC: E60 + C600	560	46 40 p = NS	NA	NA
Carmichael et al, 2001 [17]	ET: E75 + T200 EC: E75 + C600	705	67 56 p = NR	6.5 6.7 p = NS	13.8 13.7 p = NS

A = doxorubicin; C = cyclophosphamide; E = epirubicin; F = 5-flourouracil; NR = not reported; NS = not significant; ORR = objective response rate; T = paclitaxel; TTP = time to progression; NR = not reported; NA = not available.
*Doses are in mg/m^2.

Paclitaxel was first investigated with doxorubicin. While phase II trials reported impressive response rates (42–94%), an unexpectedly high incidence of congestive heart failure (>20%) was seen in some of the studies, particularly when reaching a cumulative dose of doxorubicin of 360 mg/m^2.[11,12] Further investigation revealed a pharmacokinetic interaction between paclitaxel when given over three hours and doxorubicin; paclitaxel decreases the hepatic metabolism of the anthracycline and its metabolites, increasing as a consequence, the anthracycline area under the curve (AUC).[13] Various strategies were therefore developed to prevent the cardiotoxicity, ranging from:

1. Limiting the cumulative dose of doxorubicin to 360 mg/m^2

   to

2. Increasing the interval between the infusion of the drugs (16 hours or more),

   or

3. Administering one or both drugs with prolonged infusions.

Several randomized trials have compared paclitaxel/anthracycline combinations to other programs in MBC (Table 2). In the intergroup trial,[6] paclitaxel-doxorubicin produced higher response rates (46% versus 33–34%) and time to progression (TTP) (8.0 versus 5.9–6.2 months) than either agent alone, but without advantage in overall survival, mostly related to the built-in crossover. In another trial comparing doxorubicin (FAC) with the paclitaxel/doxorubicin doublet, with 24 hours' interval between the delivery of paclitaxel and doxorubicin, response rates (68% versus 55%), TTP (8.3 versus 6.2 months), and overall survival (23.3 versus 18.3 months) were superior in the taxane-containing arm.[14]