International Journal of Clinical Medicine, 2016, 7, 419-432
Published Online June 2016 in SciRes. http://www.scirp.org/journal/ijcm
http://dx.doi.org/10.4236/ijcm.2016.76044

Rationalizing Optimal Timing for Adjuvant Hormone Therapy for Patients with Breast Cancer: Impact on Limited Resource Countries

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Received 9 April 2016; accepted 27 June 2016; published 30 June 2016

Abstract

Modern day cancer chemotherapy is complex and involves multiple drugs given either sequentially or concurrently, as an adjuvant or neo-adjuvant. Besides the concentration of the drug, timing, duration and sequencing of individual drugs in combination with other similar agents play a vital role in the final therapeutic outcome. This study constitutes an exhaustive overview of current knowledge of timing and sequencing, specifically of Tamoxifen, based on tumor's hormone receptor status, as part of a comprehensive treatment plan. It has become apparent that inappropriate timing or sequencing can be detrimental. On the other hand, appropriate timing and sequencing of Tamoxifen, based on breast cancer cell-biology, pharmacokinetics and pharmacodynamics of drugs, the body's homeostatic response to drugs; surgery and radiation, yield huge benefit for locoregional control, long-term survival and reducing complications in patients with breast cancer. *Conclusion*: A rational plan for use of Tamoxifen has been recommended, based on this study; for optimal therapeutic benefit. It has also been suggested that in receptor "unknown cases", it is beneficial to prescribe Tamoxifen, since 75% of breast cancers are likely to be estrogen receptor positive and side effects can be minimized with planned vigilance.

Keywords

Optimization, Tamoxifen, Breast Cancer, Limited Resource Countries

1. Introduction

Tamoxifen (estrogen receptor modulator) and Letrozole (an aromatase inhibitor) are used extensively for ER

How to cite this paper: Malaker, K. (2016) Rationalizing Optimal Timing for Adjuvant Hormone Therapy for Patients with Breast Cancer: Impact on Limited Resource Countries. *International Journal of Clinical Medicine*, **7**, 419-432.
http://dx.doi.org/10.4236/ijcm.2016.76044

and PR receptor positive, for both pre- and post-menopausal patients, with breast cancer. In an adjuvant setting, when Tamoxifen is used as part of treatment, the optimum timing of sequencing hormones with chemotherapy, radiotherapy and surgery has been frequently queried.

On the clinic floor, the appropriate time to start and stop hormones if prescribed and the ability to stop at any time, if at all, or until the regimen finishes, are often asked by both patients and nursing staff alike.

The majority of cancer treatments involve multiple chemotherapy agents and multiple treatment modalities. Due to variable interaction with hormones and other therapeutic agents, it is important to have a clear understanding of the optimum dosage, sequencing and timing of each agent and each modality. This is likely to have a profound impact on the final outcome.

Optimizing time and sequence of surgery, radiotherapy and chemotherapy in the management of breast cancer can improve therapeutic benefits [1]. The addition of hormones and anti-hormones to breast cancer treatment armamentarium has improved the total outcome significantly [2] [3].

Sequencing chemotherapy with radiation and surgery for patients with breast cancer has been well studied in classical investigative work by Abraham Recht [1] Adjuvant chemotherapy, adjuvant radiotherapy, preoperative chemotherapy/radiotherapy, radiotherapy sandwiched between cycles of chemotherapy, and neo-adjuvant chemotherapy all have been extensively studied by many investigators following Recht's historical publication.

Studies to establish optimal sequencing of hormones with chemotherapy, radiotherapy and surgery appear to have generated moderate interest for clinical trials, in spite of hormones' vital role in the management of breast cancer. There have been several experimental studies [4] [5] confirming that it is worth noting that the role of Tamoxifen and estrogen on cell cycle and cell cycle dependent agents used for breast cancer may impact adversely or advantageously.

In 1981, it was proposed that adjuvant hormone therapy should be deferred during the course of chemotherapy. The simple assumption that Tamoxifen, being an estrogen receptor blocking agent, was likely to interfere with the dynamics of cycling cells, delay progression from G0 to G1 and increase in the proportion of G0/G1 phase, at the same time reducing the proportion of "S" phase. This dual effect reduces effectiveness of cell cycle dependent chemotherapy [6]. In fact, adjuvant estrogen might enhance the cell cycle and increase the proportion of "S" phase, making chemotherapy more effective [7].

The proposal at that point failed to raise intellectual curiosity. Recent rediscovery of the original proposal delighted the authors that the hypothesis is alive, being accepted (through the persistence of other investigators) and is practiced universally.

This study attempts to rationalize the importance of optimal sequencing of hormones, *i.e.*, Tamoxifen, etc., with other primary treatment modalities for breast cancer.

2. Role of Estrogen on Cell Cycle Regulation and Tumor Growth

Estrogen increases the proportion of "S" and "G2-M" phases in cycling estrogen receptor positive and negative breast cancer cell lines. The effect of platelet derived factors that initiate cell cycles crossing over from one phase to the next is influenced by estrogen. The epidermal growth factor and insulin-like growth factor stimulate cycling cells to progress from G0/G1 phase to "S" phase, which is also influenced by estrogen [8]. Thus, estrogen itself, by promoting cell cycle "S" phase accumulation, promotes tumor growth, invasion and metastasis.

3. Effect of Tamoxifen on the Cell Cycle

Tamoxifen, by contrast, is an estrogen-blocking agent. It exerts its anti-tumor activity by competing for and binding to cytoplasmic estrogen receptor proteins in the tumor. The drug acts as an estrogen antagonist [9]. Thus it promotes accumulation of G0/G1 phases of cycling breast cancer cells and impairs crossing over and progression forward to "S" phase. Tamoxifen retards the cell cycle by impairing the effect of growth factors on cells and reducing the effect of cell cycle dependent anti-cancer agents, *i.e.*, cytotoxic drugs and ionizing radiation. However, Tamoxifen is also known to arrest G2/M phase [10]. G2/M phase is sensitive to radiation and certain microtubule-disrupting chemotherapy agents, *i.e.*, Vincristine, Taxol, etc.

4. Cycling Cell Dependent Chemotherapy Agents

Cytotoxic cancer chemotherapeutic agents are essentially "cell cycle dependent" for their oncotoxic activity, ir-

respective of cell cycle phase dependence or independence. Chemotherapy works by killing actively growing and dividing cells. There are more dividing and metabolically active cells in cancerous tissue than its normal counterpart, which is responsible for the drug's therapeutic advantage.

Both genetic and epigenetic mechanisms are engaged in transformation of normal cells to cancer cells, affecting the orderly expression of cell cycle regulatory proteins. Transformed malignant cells have deregulated CDK activity, offering the malignant cells the advantages of faster cell cycle and growth [11]. Hence, cycling cells in "S" and "M" phases are important for chemotherapy to be effective as opposed to resting phase of G0 and G1 phase.

Any condition or agents that accumulate cells in G0 phase or arrests progression from G0 to G1 to "S" phase would inhibit the effectiveness of cancer chemotherapy. Tamoxifen does just that. Tamoxifen, by retaining more cells in G0/G1 and G2 phases of the cell cycle, induces relative resistance to the majority of cancer chemotherapy agents, compromising their therapeutic advantage [12].

5. Effect of Tamoxifen on Cycle Dependent Chemotherapy Drug Activity

From the above narrative, one can clearly deduce that Tamoxifen and other hormone receptor regulators will have a detrimental and deleterious effect on the cytotoxic function of cancer chemotherapy drugs, eventually compromising their therapeutic benefits.

On the other hand, it has been postulated that estrogen may enhance the cytotoxicity of chemotherapy drugs used for breast cancer treatment by acting as an additive or sensitizing factor by increasing percentage of "S" phase of cycling cells [13].

6. Concurrent or Sequential Tamoxifen with Chemotherapy-Clinical Studies (Table 1)

The debate of concurrent or sequential use of hormones, especially Tamoxifen and chemotherapy, is reasonably settled. Clinical studies (**Table 1**) indicated that due to the cytostatic effect of Tamoxifen and other associated hormones used for cancer treatment, it is better given sequentially and not concurrently. As discussed above, concurrent usage of hormones is likely to compromise the cytotoxic effect of cancer chemotherapy, which is dependent on cycling cells especially on the "S" phase component.

Table 1. Chemotherapy—hormone therapy; concomitant or sequential clinical studies.

Author	Type of study	Conclusion
Gradishar W, *et al*. (2006) [2]	Analysis: multiple prospective study	Sequential recommended: Tamoxifen & Anastozole Combo is better
Baum M, 1988 [3]	Global multi-centric prospective	Adjuvant Tamoxifen on pre & postmenopausal Advantage: No comment on CON V SEQ
Pritchard KI, 2008 [14]	Review & Reflective	Hormone with chemo; CON V SEQ: yet a matter of debate
Albain K, *et al*. 2002 [15]	Prospective & Randomized	Should be "sequenced not concurrent"
Pico C, *et al*. 2004 [16]	Trend in favor of sequential	Trend in favor of sequential
Bedgonetti D, *et al*. 2011 [17]	Prospective & Randomized	No diff: CON V SEQ: Poor statistical power
Del Mastro L, *et al*. 2008 [18]	Prospective & Randomized	OS, DFS, Toxicity score: CON V SEQ = no difference Decreasing hazard of death-SEQ-group
Sideras K, 2010 [19]	Prospective & Randomized	Post-menopausal node +, Oe + − > SEQ more effective
Early Breast Cancer Trialists Collaborative Group (EBCTCG) 2005 [20]	Prospective & Randomized 145,000 pt—15 yr FU	CT + SEQ Tam significantly better than CT + No Tam CON V SEQ − not recorded

7. Effect of Tamoxifen on Cycle Dependent Chemotherapy Drug Activity

Ionizing radiation used for radiotherapy is essentially independent of cell cycle or cycling cells. It damages cells indiscriminately, irrespective of their malignant, benign or normal physiological status. Ionizing radiation damages cells by both intracellular and extracellular events. They are known as "4R" *i.e*., repair, re-oxygenation, redistribution and repopulation. None of these effects are cycling cell dependent. The events happen after the cells have been irradiated and the 4Rs conjointly sum up the final outcome of radiation on cancer cells. Irrespective of whether the cells are cycling or not. However, in cycling cells, phases G2 and M are relatively more radiosensitive; likely due to a higher number of target sites, prone to get damaged from ionizing radiation. As far as DNA strand break, that causes cellular radiation effects that are similar on individual DNA strands irrespective of the phase of the cell cycle [21].

8. Effect of Tamoxifen on Radiation Effects on Cancer Cells

As Tamoxifen increases percentage of G0/G1 phases, it will have a neutral impact on the cytotoxic effect of ionizing radiation. On the other hand, Tamoxifen also increases G2/M phases by blocking progress. It increases the number of apoptotic cells which are more radiosensitive than other phases likely due to the increased number of targets. Thus, the final outcome is a positive balance in favor of Tamoxifen concurrently administered with radiotherapy, which is likely to act as a radio-sensitizer [22].

9. Concurrent or Sequential Adjuvant Therapy of Tamoxifen and Other Hormones with Radiotherapy (Table 2)

Sequential or concurrent hormone therapy with radiotherapy for breast cancer is currently being debated. With the laboratory experimental clinical trials, the balance is in favor of concurrent usage of Tamoxifen with radiotherapy. It is important to get the best timing for hormonal adjuvant with radiation therapy, since hormones are

Table 2. Adjuvant concurrent vs sequential hormone therapy with radiotherapy: clinical studies and clinical study review.

Author	Type of study	Conclusion
Harris EE, *et al*. 2005 [24]	Retrospective 278 patients	No clinical impact on cosmesis, complication either modality: No comments on CON V SEQ
Azria D, *et al*. 2005 [25]	Commentary (retrospective data)	"Concurrent" increases subcutaneous and pulmonary fibrosis
Azria D, *et al*. 2004 [26]	Retrospective 147 patients	"Concomitant"-Tamoxifen (Tam) increases sub-cut breast fibrosis in hypersensitive patients
Whelan T, *et al*. 2005 [27]	Editorial review	SEQ or CON: yet to be resolved Randomized trial recommended
Pierce LJ, *et al*. 2005 [28]	Prospective randomized, 309 pts	No difference in adverse effect, local or systemic recurrence RT + TAM or RT only
Ismail SS, *et al*. 2013 [29]	Prospective 160 patients	No difference RT + CON or SEQ
Bentzen SM, *et al*. 1996 [30]	Retrospective 84 patients	Increase in lung fibrosis in CON Group
Ishitobi M, *et al*. 2009 [31]	Retrospective 264 patients	No difference between CON and SEQ Group
Tsoutsou PG, *et al*. 2010 [32]	Review	May be given CON or SEQ (RT) Combination of Tamoxifen and Letrozole recommended
Ahn PH, *et al*. 2005 [33]	Retrospective 495 patients	CON did not affect local control No observation on cosmesis and toxicity
Koc M, *et al*. 2002 [34]	Prospective 111 patients	RT + TAM V RT + 0: Tele cobalt RT Significant risk of lung fibrosis. No comment on CON V SEQ
Cecchini MJ, *et al*. 2015 [35]	Literature review	SEQ supported due to increase in lung fibrosis in CON treatment
Munshi A, *et al*. 2011 [36]	Randomized prospective	Results awaited (major study)

given for a period of 5 to 10 years. It is possible that minor but avoidable side effects from either choice might magnify to be a major clinical issue over a prolonged treatment period. **Table 2** lists clinical and experimental findings to assist in developing a consensus of optimal use of hormones with radiotherapy for breast cancer patients.

10. Effect of Surgery on Cancer Cell Kinetics

Hippocratic physicians from the 5th century BC through 7th century AD believed that ulcerated breast lesions were likely to recur more aggressively if resected, than those which did not present with ulceration [23]. Even though the conventional wisdom had been not to operate on cancerous breast lesions to avoid faster recurrence and spread, with the advent of anesthesia, surgical techniques became wider and more extensive without any real benefit for either relapse or survival. Several clinical studies did indicate that post-surgical residual cancer and dormant cancer cells are activated following surgical excision, growing faster and metastasizing more widely with virulence (**Table 3**).

A wide range of experimental research indicated the rapid growth of lung metastasis following resection of leg sarcoma [3], increased vascularity and reduced apoptotic cells in post-colectomy hepatic metastasis in rats [14]. Surgical trauma's responsibility for post-mastectomy recurrence and spread was reiterated by mathematical models in animals [15]. There was also post-surgical spiking of the labeling index (LI) in experimental tumors [16], post-surgical increase in residual tumor size, progression to proliferative phase and synchronization to sensitive phases in experimental system [17] (**Table 3**, **Table 4**). Experimental studies also indicated the essential role of tumor stroma in carcinogenesis, prevention of neoplastic development and functional dedifferentiation of breast cancer cells into normal ductal growth [18] [19] (**Table 4**). As an important extra-cellular effect of Tamoxifen, irrespective of estrogen receptor status, Tamoxifen interacts with the stromal-fibroblasts of human breast cancer and induces production of TGF beta1 (TGF B family), which is a novel receptor-independent action of Tamoxifen. This function of Tamoxifen is a potent inhibitor for the epithelial cell cycle, hence progression and growth of breast cancer [53] [54].

Several clinical and clinicopathological studies indicated: cytoreductive surgery for testicular tumors, enhanced tumor progression [20], and post-surgical accelerated growth of metastasis in non-small cell lung cancer [22]. Improved survival and relapse following Laparoscopic cholecystectomy compared to open cholecystectomy

Table 3. Clinical, clinicopathological and experimental studies: surgery + concomitant versus Sequential use of hormone in treatment of cancer patient.

Author	Type of study	Conclusion
Demicheli R, *et al.* 1997 [37]	Experimental Mathematical Model	Two peaks after resection. Surgical trauma, essential to manifest the peaks of recurrences
Peters CFJM, *et al*. 2006 [38]	Experimental & Clinicopathological	After partial liver resection, residual tumor shows aggressive and faster recurrence
Schatten WE, 1958 [39]	Experimental	Rapid growth of large number of latent pulmonary metastasis after removal of primary in leg
Lange PH, *et al.* 1980 [40]	Retrospective Pathological & Serological	Tumor progressed after cytoreductive surgery: clinical trial urged. Post resection recurrence of testicular tumors
Demicheli R, *et al*. 2008 [41]	Review & Critical Appraisal	From tumor dormancy to surgery driven enhancement of growth and metastasis likely
Baum M, *et al*. 2005 [42]	Review & Critical Appraisal	Surgery induced angiogenesis and proliferation of distant dormant micro-metastasis
Lacy AM, *et al*. 2002 [43]	Randomized Prospective	Laparoscopy assisted colectomy is superior than open colectomy; Morbidity, hospital stay, recurrence and Ca-related death, less: due to less surgical tissue damage
Mitsudomi T, *et al.* 1996 [44]	Retrospective	Post-surgical accelerated growth of undetectable residual cancer and dormant cancer cells
Gunduz N, *et al.* 1979 [45]	Retrospective	Post-surgical increase in residual tumor size; conversion of G0 to proliferative phase; synchronization of sensitive phases
Fisher B, *et al*. 1983 [46]	Experimental	Labelling Index (LI) peaks 3 days after tumor excision; Perioperative chemotherapy recommended

Table 4. Biological changes in post-operative environment: clinical and experimental findings.

Author	Type of study	Conclusion
Maniwa Y, *et al*. 1998 [47]	Clinical & Experimental	Disruption of angiogenesis suppression, induction of growth of dormant micro-metastasis due to post-op increase in VEGF
Ikeda M, *et al*. 2002 [48]	Clinical	Peri-gastrectomy serum concentration of VEGF, sP-selectin, v WF, involved in angiogenesis, tumor-platelet adhesion, tumor-endothelial cell adhesion factors; surgical intervention enhanced tumor growth and metastasis
Tagliabue E, *et al*. 2003 [49]	Clinical-operative specimen	HER2 over-expression by breast ca cells plays in post-surgery stimulation of growth of breast cancer cells
Wu FP, *et al*. 2003 [50]	Prospective Patho-physio, Cancer v normal tissue, 16 specimens	Local VEGF increase & endostatin decrease; physiological response to surgery, with or without cancer
Mitsudomi T, *et al*. 1996 [44]	Retrospective Clinical (197 cases)	Concluded residual tumor cells had accelerated growth after surgery
Maffani MV, *et al*. 2004 [51]	Experimental	Important role of tumor stroma indicated; further extensive study recommended
Maffani MV, *et al*. 2005 [52]	Experimental	Rat mammary gland tumor stroma prevents neoplastic development and encourage normal ductal growth from grafted epithelial cancer cells

suggests surgical trauma or lack of it is a responsible factor [24], as are disruptions of tumor-host homeostasis and activation of dormant cells [25], etc. Clinical and experimental studies indicated, post-operative increase in VEGF and a decrease in endostatin [27]. VEGF-induced angiogenesis stimulates growth of micro-metastasis [25] [26]. Post-gastrectomy increase in angiogenic factor, tumor-platelet adhesion factor, and tumor-endothelial cell adhesion factor influence tumor growth and metastasis [26] and post-surgical over-expression of HER2, stimulating cancer cell growth [35] (**Table 4**). Illustrated **Figure 1** and **Figure 2** indicates a possible existing dynamic tumor-host homeostasis (anticipate inherent changing balance by mutual consent) and results of disruption caused by surgical excision of the tumor, initiated by the "Substrate Vacuum" *i.e*., loss of the tumor mass, loss of stromal control on tumor growth and reduction of metastasis.

11. Effect of Tamoxifen on Surgery Induced Changes in Cancer Cell Kinetics

Having extensively reviewed clinical, clinic-pathological and experimental findings, the changes induced by Tamoxifen in post-operative surgical environment is getting clearer. The result of surgery alone in patients with cancer is essentially undesirable, except very small tumors which are yet to develop; a form of biological dynamic symbiosis between the tumor and host environment.

Strong evidences are now available to support the 2500-year-old Hippocratic dictum, not to operate on breast lesions which have ulcerated, because it regrows fast and spreads faster. We have enough striking evidence (**Table 3**, **Table 4**) to support the notion that postoperative loss of homeostatic balance between the tumor and the noncancerous elements, especially the stroma, induces residual cancer regrowth faster; micro-metastasis and dormant cancer cells are reactivated, changing to fast-proliferating, fast-metastasizing invasive cells. Surgical loss of stromal elements of the tumor, which commands significant influence on suppression of tumor proliferation, also negatively affects post-operative tumor control.

Hormones, *i.e*., Tamoxifen, which arrest cycling cells at G0 and G2 phases from progressing to G1 and M phases, respectively, are less likely to be affected by the post-operative perturbation of tumor-host homeostasis that induces accelerated tumor growth and metastasis. Thus perioperative use of Tamoxifen will prevent or reduce surgery induced accelerated residual tumor proliferation and metastasis. Also Non-hormonal control of Tamoxifen, tumor proliferation, with the help of tumor and normal stromal components, that aids retarding post-operative tumor recurrence and proliferation.

12. Recommendation of Sequencing Hormones with Other Therapeutic Agents

To rationalize sequencing Tamoxifen-like hormones, with other modalities, one needs to consider pharmacokinetics and pharmacodynamics of the hormone. Tamoxifen peaks at around 5 hours after a single oral use. To achieve a steady state plasma concentration, it takes 4 weeks, while on daily oral intake. The biphasic decline of

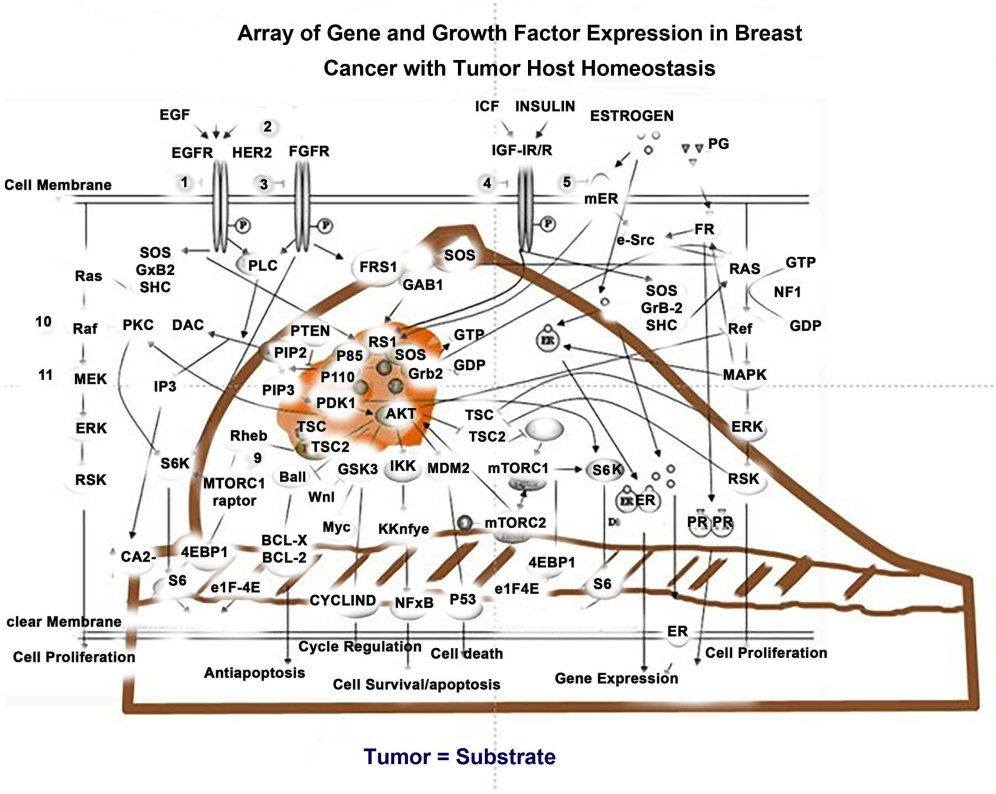

Figure 1. Array of gene and growth factor expression in breast cancer with tumor host homeostasis.

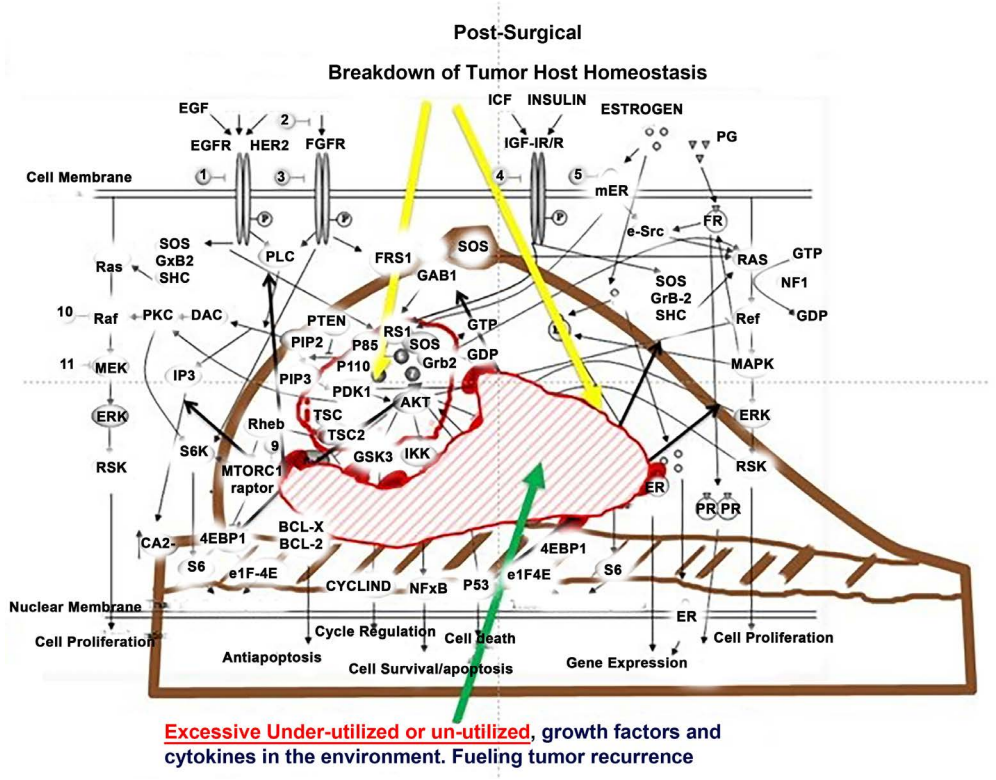

Figure 2. Post-surgical breakdown of tumor-host homeostasis and loss of stromal interaction.

plasma concentration pattern accounts for its biological half-life of 5 - 7 days. Sixty-five percent is excreted through feces over 14 days [54] [55].

Hence one needs to be aware of the pharmacology and biological effect of hormones used as adjuvants to a multimodality treatment plan, as well as the effect of Tamoxifen on the kinetics of the tumor itself and its impact on an individual agent's biological action on growth and metabolic kinetics of the targeted tumor. Thus an essentially pharmacological approach will impact the aggregate effect of multi-modality agents on the final outcome of hormonal adjuvant.

12.1. Tamoxifen and Chemotherapy

Tamoxifen and, for that matter, other cytostatic anti-hormonal agents, it is apparent from the above overview, act against the cytotoxic effect of chemotherapy drugs and would compromise the therapeutic benefit of chemotherapy. Tamoxifen should be stopped at least 7 days before commencement of chemotherapy. It needs to be resumed soon after (1 - 3 days), depending on chemotherapy drug elimination rate, and as soon as the prescribed cycle is completed. Hence, Tamoxifen and other cytostatic anti-hormones should be used sequentially with chemotherapy and not concurrently.

12.2. Tamoxifen and Radiotherapy

From the above overview, it appears that the biological impact of Tamoxifen on radiotherapy has been protective (detrimental) against radiotherapy due to G0/G1 block; also, cells in G0/G1 phase are relatively resistant to DNA damage due to a higher ability to repair. On the other hand, Tamoxifen induced G2-M delay/block has a sensitizing effect on radiotherapy, likely due to a higher number of target sites. The composite effect of Tamoxifen and, for that matter, aromatase-inhibitors have moderate radio sensitizing benefit. Unfortunately, this advantage is counterbalanced by the excessive fibrosis of lung and breast tissue (perhaps other sites too) post-concurrent Tamoxifen-radiotherapy treatment for breast cancer. This is an important fact to note in developing countries where radiotherapy is given mostly in tele-cobalt units, which do induce higher post-radiation fibrosis as compared to treatment by Linear Accelerators. Concurrent use of Tamoxifen with tele-cobalt generated radiotherapy, without any doubt, will exacerbate fibrosis of lung, chest wall, and the preserved breast after limited resection. Some individuals are sensitive to radiation, if detected, they should also not be given Tamoxifen concurrently with radiotherapy. A simple Lymphocyte-sensitive test can reasonably detect radiosensitive individuals. Otherwise some physical features, *i.e.*, people with blue eye, red hair, Irish-freckles, and people with tuberal sclerosis, xeroderma pigmentosa are known to be radiosensitive, should not be given tamoxifen concurrent with radiotherapy.

Thus, it is fair to use Tamoxifen sequentially with radiotherapy and not concurrently. Tamoxifen needs to be stopped 5 - 7 days (expected serum level to be lower than steady state, hence reduced bio-availability) prior to commencement of radiotherapy and resume couple of days after the last fraction of radiotherapy.

12.3. Tamoxifen and Surgery

From the above review, it is apparent that surgery does impact negatively on tumor control by accelerating proliferation of residuum and activating growth and metastasis of "dormant" microscopic non-proliferating tumor components. Tamoxifen and other cytostatic anti-hormone agents can inhibit to some extent this "blast" of post-operative tumor proliferative activities by retaining cells in the non-proliferative phase (G0/G1, G2-M). Hence, Tamoxifen and other cytostatic anti-hormones should be started 2 - 4 weeks prior to surgery and continued until there is a therapeutic reason to stop or pause.

Therefore, as soon as a tissue diagnosis confirms malignancy of the breast, even before the receptor results are available, it is recommended that Tamoxifen or Letrozole in post-menopausal patients be started to control tumor growth. It can be stopped if the receptors are reported to be negative, as and if they are available. The non-hormonal extra-cellular activity of Tamoxifen and Tamoxifen-stromal interactive-influence on suppression of cellular proliferation will also have a positive impact.

13. Limited Resource Countries-Optimizing Adjuvant Tamoxifen (Other Such Hormones Used for Adjuvant Treatment for Breast Cancer)

In developing countries, where resources are scarce and there is delay in getting the desirable surgery, a delay in

obtaining chemotherapy agents, a delay or non-availability of radiotherapy or even unavailability of "receptor status"; it is prudent to start Tamoxifen for all premenopausal and Letrozole to postmenopausal patients with biopsy proven breast cancer, prior to any definitive therapy, unless there is a preexisting clinical condition that dictates otherwise. Tamoxifen is inexpensive and generally available even in the developing world. Its side effects are minimal and can be monitored by a general practitioner and periodically by Gynecologists, not necessarily a Gynecological-Oncologist.

In receptor "unavailable" cases, the tumor being "receptor positive" is around 75% in pre-menopausal and higher in post-menopausal cases [56]. The extra-hormonal, extracellular, anti-breast cancer activity of Tamoxifen should also be taken into account. This essentially ignored function of Tamoxifen does add to the anti-cancer activity, irrespective of "receptor status". The advantages of adding Tamoxifen to the armamentarium of breast cancer treatment far outweigh the disadvantages and risks in receptor "unavailable" cases [57] [58]. Tamoxifen does reduce recurrences in the affected breast and also in the contralateral breast with DCIS, following lumpectomy and radiation; irrespective of receptor status [59].

Specifically, it is worth reiterating that the majority of developing countries' radiotherapy is delivered by tele-cobalt treatment unit. Extra effort should be made to ensure that Tamoxifen is stopped 1 - 2 weeks prior to starting radiotherapy and resumes 2 days after the last fraction, to minimize soft tissue post-radiation fibrosis (by this period, serum levels would have been reduced to an acceptable steady state, appropriate for the need).

As far as sequencing of Tamoxifen and like agents (Letrozole) for chemotherapy and surgery is concerned, evidence suggests the sequencing may be carried out as per resource rich countries, recommended in this overview.

While the developing world pines for acquisition of high tech, high cost, complex technology, and expertise-dependent interventions, that remains a wishful desire. These may be common in the developed world, but are unlikely to be available in limited resource countries. At the same time, LRC miss the simple adjustment to practice that may impact them profoundly; appreciation of a simple management strategy like "Optimizing Tamoxifen Sequencing" for breast cancer, as well as other neglected biological phenomena like "utilization of diurnal variation of drug effectiveness" and simpler technology utilizing "hyperthermia" to enhance the oncotoxic effect of other modalities, the scope of inhalation chemotherapy, etc. There are many other examples whose aggregate effect may supersede the therapeutic impact of most modern complex technological advances for cancer management.

14. Conclusions (Figure 3 for Graphic Recommendation)

It is a standard practice to prescribe Tamoxifen for hormone receptor positive patients with breast cancer. Immunohistochemical assay for hormone receptor of breast cancer is expensive and beyond reach for most "resource limited" regions, where eighty percent of world's population lives. However, the benefit of using Tamoxifen as an adjuvant treatment for "receptor unknown" cases of breast cancer far outweighs the dangers of recurrence and spread. Tamoxifen is far more readily available in resource limited country than the availability of immunohistochemical test. Hence, it is advised that irrespective of the "receptor status" all women with breast cancer can be placed on Tamoxifen or like, as long as there are no preexisting risk factors like, history of coagulopathy, DVT, diabetes, extensive varicosity etc.

It is suggested that as soon as histopathological diagnosis of primary breast cancer is confirmed, patients should be started on Tamoxifen (Letrozole for postmenopausal). Then, the plan should be amended when or if the receptor status becomes available.

Patients should continue Tamoxifen throughout the course of planned surgical management.

If radiotherapy is planned, Tamoxifen should be stopped 7 days prior to starting radiotherapy. If the patient is found to be radiosensitive on a Lymphocyte sensitivity test (a simple, but very useful test) or the patient has physical features of radio sensitivity *i.e.*, blue eyes, red hair, skin with excessive freckles; then there should be restrictions. Even mixed races with above features would have these restrictions. If suspended, then Tamoxifen should be started on the last day of radiotherapy. Otherwise Tamoxifen should be continued throughout the course of radiotherapy.

If chemotherapy is planned; Tamoxifen should be stopped 7 days prior to starting of chemotherapy and resume 2 days after the last infusion of chemotherapy. By that time, the effective role of chemotherapy would have waned.

Patients who are placed on Tamoxifen should be regularly checked by both an oncologist and gynecologist.

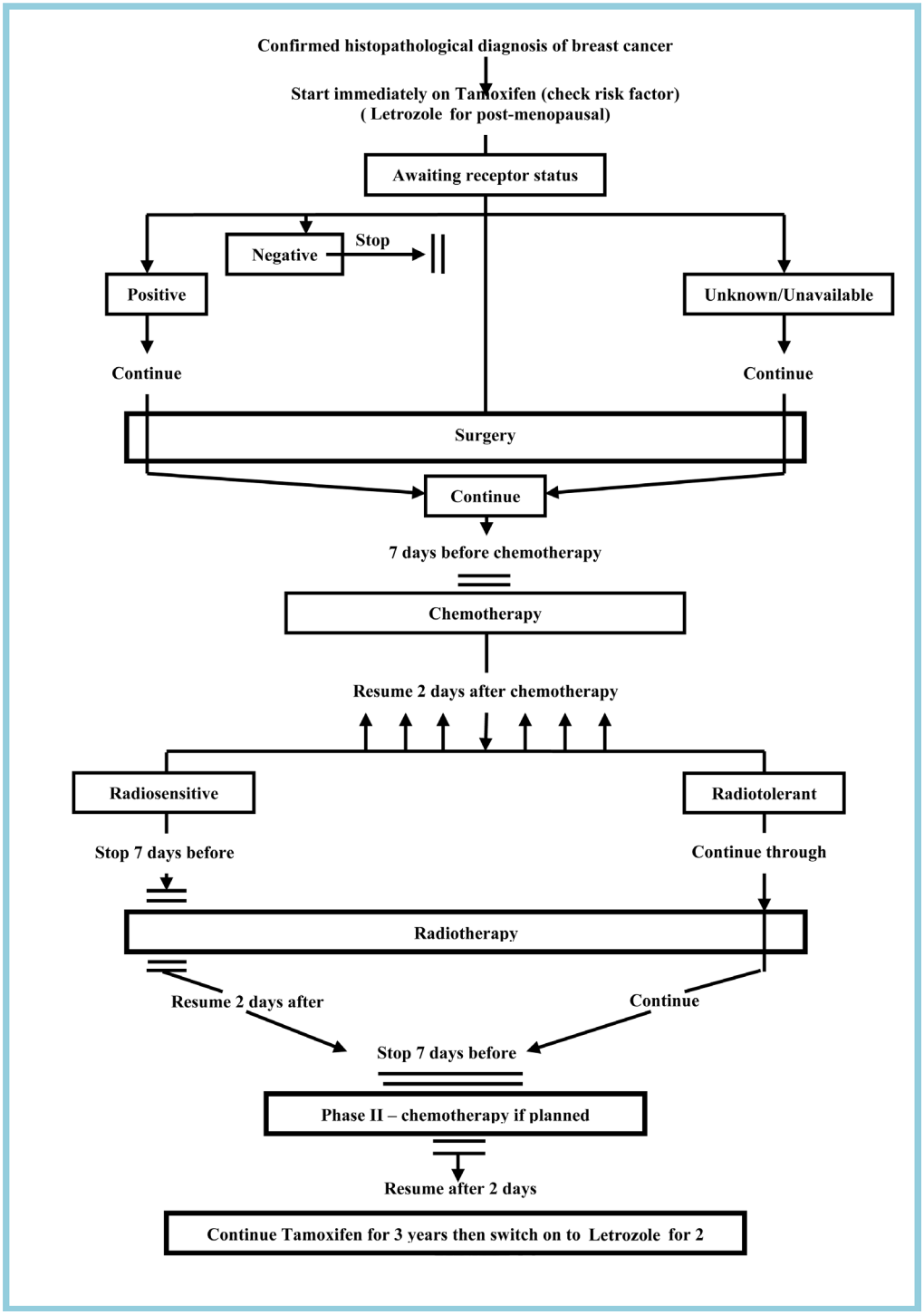

Figure 3. Comprehensive schema of Tamoxifen (Letrozole) during multimodality therapy and follow-up.

Acknowledgements

To Prof Dr Gerald Grell, friend & critique, Dr Ruby Blanc, Medical director of Princess Margaret Hospital; all my patients at the clinic who questioned about the hormones, my physician colleagues, the nursing staff including Sister Sharon Darroux Francis, Nurse Clara Richards and Nurse Aisha Darroux who are ever vigilant on timing of Tamoxifen and Amina Toussaint for secretarial assistance.

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