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Alternate dosing schedules for cancer chemopreventive agents

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ABSTRACT

Pharmacologic interventions for cancer risk reduction involve the chronic administration of synthetic or natural agents to reduce or delay the occurrence of malignancy. Despite the strong evidence for a favorable risk-benefit ratio for a number of agents in several common malignancies such as breast and prostate cancer, the public's attitude toward cancer chemoprevention remains ambivalent, with the issue of toxicity associated with drugs being perceived as the main barrier to widespread use of preventive therapy by high-risk subjects. Among the strategies to overcome such obstacles to preventive therapies, two novel and potentially safer modes of administering agents are discussed in this paper. The first strategy is to lower the dose of drugs that are in common use in the adjuvant setting based on the notion that prevention of cancer cells from developing should require a lower dose than eradicating established tumor cells. A second approach is to adopt an intermittent administration similar to what is used in the chemotherapy setting in an attempt to minimize risks while retaining benefits. This article provides a detailed discussion of the principles and future development of these two approaches in the direction of a precision preventive medicine.

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1. Introduction

Cancer chemoprevention is the use of natural, synthetic, or biologic (from a living source) substances to either prevent DNA damage that might enhance carcinogenesis or suppress the appearance of the cancer phenotype [1]. Tremendous efforts are being made to prevent and treat all forms of cancer, especially breast, prostate, and colorectal neoplasia. Tamoxifen is the only proven oral agent for the adjuvant hormonal treatment of hormone receptor (HR)-positive breast cancer in premenopausal women [2], and it can be used for prevention in both pre- and postmenopausal women who are at increased risk of breast cancer [3]. However, the toxicities of tamoxifen, such as thromboembolic events and endometrial cancer, still pose a clinically significant problem overall, especially in the prevention setting. One strategy to reduce the adverse side effects of tamoxifen, while still retaining its beneficial anti-cancer properties has been to examine the efficacy of lower doses, which are anticipated to be associated with lower toxicity. Notably, and surprisingly overlooked, in the first clinical trial of tamoxifen ever performed in advanced breast cancer, there was a trend to a higher response rate with 10 mg/d versus 10 mg twice daily (36% *v* 17%) [4]. However, the dose of 20 mg daily has become the standard dose in all treatment settings including prevention since 1973 [5].

Another way to potentially reduce long-term toxicity would be to use intermittent dosing schedules. In 2011, Wu and Lippman developed a new concept called "short-term intermittent therapy to eliminate premalignancy" (SITEP) [6]. Intermittent dosing schedules would be able to reduce serious long-term adverse effects while retaining efficacy. The mechanism hypothesized is the elimination of premalignant cells via apoptosis induced by synthetic lethal interactions, allowing selective elimination of premalignant clones without harming normal cells [6].

In the present review we will discuss the results of the studies which prompted the introduction in 2004 of low-dose tamoxifen in different forms, 5 mg/d or 10 mg on alternate days or 20 mg per week, into the European Institute of Oncology (EIO) clinical guidelines for management of hormone-responsive ductal carcinoma in situ of the breast (Table 1). This review will summarize the tremendous growth of knowledge that has taken place in this field, with a focus on what we have learned from the clinical trials performed by our group, as well as the potential direction of future research in this area with drugs other than tamoxifen. Finally, we will mention briefly the concept of intermittent dosing in cancer prevention, which has been discussed for many years, but reports of this approach in the scientific literature are rather limited.

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Table 1
Study results for the selective estrogen receptor modulator tamoxifen as a potential preventive agent for breast cancer.

Author, year	Treatment	# Patients	Population	Primary endpoint	Comment
Cole MP et al 1971 [4]	TAM 10 mg/d TAM 20 mg/d	46	Women with advanced BC	Response rate	Of the 11 receiving lower dose, 4 were classed as responders. No evidence for a dose-response relationship.
DeCensi et al 1998 [13,38]	Placebo TAM 20 mg/d TAM 10 mg/d TAM 10 mg/ alternate days	127	Healthy women Hysterectomized 35–70 years	Total cholesterol (primary) Surrogate markers of cardiovascular disease, IGF-I	Up to a 75% reduction in the conventional dose of tamoxifen (20 mg/d) does not affect the activity of the drug on a large number of biomarkers.
de Lima *et al* 2003 [25]	Placebo TAM 5 mg/d TAM 10 mg/d TAM 20 mg/d	56	Premenopausal women with a diagnosis of fibroadenoma of the breast	ER, PgR, Ki-67	Lower dose of tamoxifen can reduce the side-effects associated with treatment without affecting its chemopreventive activity in the breast.
DeCensi et al 2003 [26] DeCensi et al 2010 (f-up) [22]	TAM 1 mg/d TAM 5 mg/d TAM 20 mg/d	120	Presurgical trial in ER+, BC patients	Ki-67 modulation	Ki-67 expression decreased to a similar degree among the three tamoxifen dose groups. Ki-67 expression after short-term tamoxifen is a good predictor of recurrence-free survival and overall survival.
DeCensi et al 2009 [32]	TAM 5 mg/d FEN 200 mg/d TAM+FEN Placebo	235	Premenopausal women pT1mic/pT1a BC; OR Intraepithelial neoplasia; OR Gail risk at5years $>1.3\%$	Plasma IGF-I; Mammographic density; Uterine effects; Breast neoplastic events after 5.5 years	Despite favorable effects on plasma IGF-I levels and mammographic density, the combination of low-dose tamoxifen plus fenretinide did not reduce breast neoplastic events.
Bonanni et al 2009 [38]	ANA 1 mg/d TAM 10 mg/wk ANA + TAM	75	Postmenopausal women with previous breast intraepithelial neoplasia	Plasma drug concentrations Biomarkers' modulation	The addition of a weekly tamoxifen administration did not impair anastrozole bioavailability and modulated favorably its safety profile.
DeCensi et al 2007 [42]	TAM 1 mg/d TAM 5 mg/d TAM 10 mg/wk Placebo	210	Current or de novo HRT users	IGF-I	IGF-I declined in all tamoxifen arms ($P = .005$), with a greater change on 5 mg/d. Tamoxifen did not increase endometrial Ki-67 expression.
Guerrieri Gonzaga et al 2010 [47]	TAM 20 mg/wk TAM 5 mg/d	983	Women with Previous DIN	Second primary breast cancer (in situ or invasive)	Low-dose tamoxifen is a promising and safe strategy for highly endocrine responsive DIN. Treatment adherence is crucial in premenopausal women.
Ongoing [48]	TAM 5 mg/d *v* placebo for 2 yr	Estimated: 300 women	Survivors of HL	Mammographic density	
Ongoing [49]	TAM 5 mg/d *v* placebo for 3 yr	Estimated: 1,400 women	Woman operated on for lobular intraepithelial neoplasia or ER-positive DIN	Incidence of invasive breast cancer and ductal carcinoma in situ	

TAM, Tamoxifen; ER+, estrogen receptor–positive; BC, breast cancer; IGF-I, insulin-like grow factor I; HRT, hormone replacement therapy; FEN, fenretinide; ANA, anastrozole; DIN, ductal intraepithelial neoplasia; PgR, progesterone receptor; HL, Hodgkin lymphoma.

2. Effect of oral low dose tamoxifen on circulating biomarkers of breast cancer risk

In 1996, data from animal studies indicated that reducing the tamoxifen dose to a human-equivalent dose of 1 mg/d did not diminish the drug's inhibitory activity on mammary tumor formation [7]. This finding supported the pioneering treatment trial of low-dose tamoxifen [4]. Two years later an analysis of the adjuvant tamoxifen clinical trials reported that the benefits of tamoxifen in terms of both recurrence and mortality appeared to be about as big in the trials of 20 mg/d as in the trials of 30–40 mg/d [8]. Taking into account the long plasma half-life of tamoxifen which ranges from 4–11 days after the steady state is reached [9], and given the consistent data from adjuvant therapy trials of an increasing risk of endometrial cancer with duration of use and also with cumulative dose [10–12], both a reduction of dosage and an intermittent administration offer plausible ways to improve the safety profile of tamoxifen. Thus, lower doses present a reasonable approach to minimizing toxicity while retaining activity.

In 1998, DeCensi et al [13] studied the effects of different doses of tamoxifen on biomarkers known to reflect its pharmacodynamic activity on different target tissues. Two experiments to assess the effect of low-dose tamoxifen in 127 healthy hysterectomized women aged 35–70 years were performed. Women were randomly assigned to placebo (n = 31) or tamoxifen 20 mg/d (n=30) (first experiment); and tamoxifen 10 mg/d (n = 34) or tamoxifen 10 mg/alternate days (n = 32) (second experiment) [13]. Baseline and 2-month measurements were compared for total cholesterol (primary endpoint) and other surrogate markers of cardiovascular disease and, in a subgroup of 103 women, insulin-like growth factor (IGF)-I, implicated as a putative surrogate biomarker of breast cancer risk [14,15], was also assessed. Reduction in the conventional dose of tamoxifen (20 mg/d) by up to 75% did not affect the activity of the drug. In particular, the reductions in

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