Tamoxifen (TAM): the dispute goes on

Sandro Grilli
Dipartimento di Patologia Sperimentale, Università degli Studi, Bologna, Italy

Summary. Tamoxifen (TAM) has been used since early '70s as antitumor agent in the adjuvant therapy of breast carcinoma. The aim was (and is) to reduce the incidence of contralateral breast cancer in primary breast cancer bearing patients. Its efficacy was about 30% when estrogen and progesterone receptors were present in the malignant breast tumor and its use in antitumor therapy is, at the present time, rather correct. Viceversa, the employment of TAM in chemoprevention of breast tumor in healthy and/or at-risk women by more than a decade has been contrasting by many scientists and supporting by others. Indeed, TAM produces not only beneficial effects but also detrimental effects (mainly induction of endometrial cancer). According to the Author of this manuscript, TAM would not be used for primary or secondary mammary tumor chemoprevention. For such purposes the right way is to wait for conclusion of ongoing clinical trials on other pure antiestrogenic agents. Indeed, good candidates to act as an antiestrogen both in breast and in endometrial tissue are under validation. In the meanwhile, the scientific dispute goes on.

Key words: tamoxifen, chemoprevention, breast carcinoma, excess risk of endometrial cancer risk, pure antiestrogens.

Riassunto *(Tamoxifen (TAM): il dibattito continua)*. Tamoxifen (TAM) è entrato in uso circa 30 anni fa come antineoplastico nella prevenzione del tumore mammario controlaterale. Si è dimostrato efficace (circa 30% di riduzione) in pazienti con tumori mammari maligni ormonoresponsivi (presenza dei recettori per ER e PR). Questo uso antitumorale non è in discussione. Viceversa l'uso come agente chemiopreventivo del tumore mammario in donne sane, a rischio normale o incrementato, è oggetto di forte disputa da oltre un decennio per gli effetti detrimentali associati a TAM, in particolare l'induzione di carcinoma endometriale. A parere dell'Autore, quindi, occorre non utilizzare TAM per questo scopo e attendere i risultati della sperimentazione clinica di molecole pure antagoniste dell'estrogeno sia nella mammella che nell'endometrio. Buoni candidati a tale effetto sono in fase di convalida. Nel frattempo la disputa scientifica continua.

Parole chiave: tamoxifen, chemioprevenzione, carcinoma mammario, rischio di carcinoma endometriale, antiestrogeni puri.

Tamoxifen (TAM) has been used since early '70s in the adjuvant hormone therapy of breast malignant carcinoma. Both single clinical studies and metanalyses performed during last two decades showed that TAM efficacy in the prevention of contralateral breast cancer was around 30% in such patients.

Due to its antitumor use, TAM employment was allowed on the basis of limited toxicological dossier which was devoid of mutagenicity and carcinogenicity properties of the molecule. Indeed, the goal of TAM employment – like that of other antiblastics which are almost all mutagenic and carcinogenic either as such or in combination and are used for many other types of human tumors – is, in the adjuvant therapy of breast cancer patients, to win the fight against the primary tumor. The overall individual excess risk for onset of a second primary iatrogenic tumor, essentially an acute non-lymphatic leukemia, is in these cases no more than 20% with a latency of the order of few decades.

For these patients that risk can be considered as rather acceptable. The same is not true when TAM is administered to healthy women.

In '80s, analytical epidemiology gave evidence of 6-fold increase in the relative risk (RR) to devolop an endometrial carcinoma in breast cancer bearing patients who daily received 40 mg TAM as hormone adjuvant therapy. Successively, the daily TAM dose was lowered to 20 mg hoping that the mechanism of action was similar to that of many non-mutagenic hormones and capable of promoting cancer only at doses (and frequencies of administration) higher than the threshold dosage and treatment duration.

Unfortunately, around ending of '80s these clinical trails showed that RR for endometrial cancer was reduced in proportion with dosage to the value of 3. In other terms, the risk was not eliminated but it was lowered linearly according to dosage. This implied to consider as possible genotoxic the mechanism of action of TAM. Estimation of excess endometrial cancer risk coming from other clinical trials performed in '90s in USA was 1.7 cases/year in 1000 malignant breast cancer bearing patients treated with TAM [1]. Thus, TAM acts as antiestrogen in the breast, blocking estrogen receptor, and, at the same time, as proestrogenic in the endometrium. TAM, therefore, causes [2, 3]:

Indirizzo per la corrispondenza (Address for correspondence): Sandro Grilli, Università degli Studi di Bologna, Dipartimento di Patologia Sperimentale, Viale Filopanti 22, I-40126, Bologna, Italy. E-mail: sandro.grilli@unibo.it.

• risks
- 3 fold increase of endometrial carcinoma using 20 mg TAM daily, the dosage which is nowadays used;
- increase of thromboembolies;
- increase of retinopathies;
- increase of rat liver tumor incidence (extrapolation to humans could not be so easy) and hepatic injury;

and
• benefits
- around 30% reduction of contralateral breast cancer tumors (and relapses);
- reduction of incidence (20%) and mortality (30%) of ischemic pathologies;
- 33% lowering of fractures.

In 1990 the Italian National Toxicology Advisory Committee (Commissione Consultiva Tossicologica Nazionale, CCTN), which Romano Zito belonged to for a very long time period, giving his personal high quality expertise and contribution, evaluated TAM carcinogenicity [4].

Such Committee invited anyone not to use TAM outside treatment of malignant neoplasia except that TAM use in rigorous, well-designed and controlled pilot clinical studies. Such recommendation aimed at contrasting the trend to generalize TAM use in breast pathology and breast tumor prevention.

Nonetheless, the concept to utilize TAM also in breast tumor prevention goes ahead after ending of the pilot study performed in UK by Powles *et al.* So, a multicentric and multistate international chemoprevention trial, named IBIS and involving UK (T. Powles), USA (B. Fisher) and Italy (U. Veronesi), started in 1992. Expected enrollment in each Country was 16 000 women to be treated with 20 mg TAM/day for 5 years *vs*. placebo [5]. The Italian arm of this study enrolled only women previously hysterectomyzed for non-neoplastic reasons, according to recommendations by CCTN. This was a caution with respect to the detrimental effect on endometrium, which was eliminated. However, a possible bias was introduced in the extrapolation of the possibly obtained results to the normal female whole population.

Simultaneously, even at the beginning of the '90s, TAM toxicological properties not investigated in '70s were studied in experimental models, especially by mutagenesis and carcinogenesis assays.

Results were, essentially, the following:

a) TAM was mutagenic in various *in vitro* and *in vivo* systems [6, 7];

b) TAM induced hepatocellular carcinoma in rats [7, 8].

The most significant TAM mutagenic effects, essentially cited in the paper by Romano Zito [8], were as follows:
- gave rise to *in vivo* DNA adducts in rat, mouse and hamster liver;
- induced UDS in rat hepatocytes *in vivo*;
- induced hepatic foci positive for GST-Pl (precursors of adenomas);
- was clastogenic both *in vitro* (micronucleus test) in human lymphoblastoid cells transfected with genes of 5 human isoenzymes of P450 cytochromes and *in vivo* in rat liver;
- induced aneuploidy, breaks and chromosomic exchanges in hepatic rat cells *in vivo* [6];
- induced mutations in codons 231 and/or 294 of p53 gene in 50% of rat hepatocellular tumors [7];
- increased gene expression of HPV-16 in a cell line from endometrial carcinoma.

TAM mutagenicity was more evident in rodents than in humans. Nevertheless, the following considerations, coming from TAM mutagenicity and applicable to ongoing clinical trials using TAM dosages lower than 20 mg/day (up to 1 mg/day) in combination with aromatase inhibitors [9], arise:
- if TAM will be equally effective at lower dosages, then risks of stochastic (mutagenic and carcinogenic) effects will be lowered in linear proportion to the dosage, even though the no effect dose can not be reached;
- such result would be, however, relevant in terms of reduction of endometrial carcinoma risk for malignant tumor bearing patients;
- it would be, on the contrary, much less relevant, as result from a first line analysis, for TAM use in chemoprevention. Indeed, TAM is a non-ideal molecule and need, in a medium-term period, substitution with an ideal (pure antiestrogen) new molecule devoid of the detrimental effects shown by TAM.

Recently, a dispute on TAM genotoxicity in terms of DNA adduct formation in human endometrial tissue was published [10].

Anyway, TAM is a genotoxic carcinogen, hence the probability of stocastic effects is directly related to its dosage.

In '90s, controversies infuriate in the scientific world while chemoprevention trials were ongoing.

Risk-benefit analyses appeared in many articles published by various journals. That happened with particular emphasis and strength in USA where Bush e Helzlsouer [11] found substantial parity between benefits and risks. Therefore, they strongly supported the indication to stop TAM chemoprevention trials.

Even Zito published a well-documented paper wholly contrary to this TAM use [8], whereas Fisher in USA asserted that benefits of TAM were higher than its risks.

Among many points and counterpoints appeared on the prestigious Journal "Science" Seachrist *et al.* [12] essentially restated risks by TAM.

However, the US arm of IBIS trial ended with around 13 000 women enrolled and a significant chemopreventive effect for breast cancer whose incidence was lowered by near 50%. The same, on the contrary, did not occur in UK and in Italy [13]. More recently, clinical research focused attention on pure antiestrogen whose characteristics would be as follows [14]:

a) antiestrogenic effect exerted in breast and endometrium;

b) proestrogenic effect exerted in bone, liver, vagina and CNS.

TAM shows proestrogenic properties for endometrium and antiestrogenic effects in breast, CNS and vagina.

Another selective estrogen receptor modulator (SERM), raloxifene, seems to be inactive or, better, to behave as

an antiestrogen in endometrium whereas, like TAM, shows antiestrogenic action in CNS and vagina. At the present time, the clinical comparison between TAM and raloxifene is ongoing through the controlled, randomized and prospective large phase III trial named STAR.

Based upon preclinical and early clinical testing and trials, many scientists hope that: a) faslodex (fulvestrant, ICI 172,780), a steroid derivative capable of blocking and degrading ER [15]; b) - anastrozole, the aromatase inhibitor under investigation in the IBIS-II study [9, 16-18] and usable as an alternative to TAM or in sequence after 2-3 years TAM treatment in order to give better results under risk:benefit profile in postmenopausal women; c) goserelin, able to block the LH release by the pituitary gland; d) COX-2 inhibitors; e) or fenretinide [19], could act as ideal antiestrogen in such a way to be used in the near future as primary or secondary chemopreventive agent for breast cancer in healthy women.

In primary chemoprevention, it will be possible to administer daily the validated chemical at non-toxic dosages to all at no excess risk women.

Secondary chemoprevention will be possible *e.g.*, in girls or young women who are at very high risk to develop a breast carcinoma in their lifetime on the basis of either genetic counselling (*e.g.*, inactivation of BRCA-1 and/or BRCA-2 genes) or histological lesions which clearly are precursors of invasive breast cancer, *i.e.* from preneoplastic nodules up to in situ carcinoma. It should be kept in mind that TAM administration or prophylactic bilateral mastectomy in oncosuppressor or DNA repair genes defective-young women or girls are not recommended first by ethical and secondly by psychological considerations. Moreover, prophylactic mastectomy reduces by 90% the risk for breast cancer onset in at high risk women [19].

Most of people and scientists are awaiting with good confidence for the availability of the ideal antiestrogen. At that time the "fight" against TAM use as chemopreventive agent will be won as strongly wished Romano Zito, along with many other experts (and friends, including the Author of this brief note) in cancer primary prevention and public heath protection.

In the meanwhile, TAM employment in breast cancer chemoprevention continues to be debated and, therefore, opinions are controversial. Some Authors think that TAM could be used in chemoprevention of at high risk women like hereditary breast cancer (RR about 20) or *in situ* lobular breast carcinoma (RR around 10). For such cases TAM use is approved in the USA [20].

At the present time:

a) TAM is the gold standard for breast cancer prevention as stated by Kramer and Rrown [21].Other Authors, on the contrary, consider also such uses as non-ethical and the dispute goes on;
b) TAM use as antitumor agent in invasive breast cancer bearing patients is rather adequate if estrogen and progesterone receptors are present in neoplastic tissue, even though improvements are expected as time passes, *e.g.* sequential use of aromatase inhibitors, new SERM, and so on.

Thus, TAM constitutes an example of: a) a reverse and wrong way to reach safety in using a drug, due to change of its use; b) toxicological data acquisition after starting of clinical trials; c) higher caution of Italian Health Ministry; d) enthusiastic adhesion of eligible women who cannot be lost or demotivated by informed consensus to be changed and signed again on the basis of new negative toxicological data and e) higher sensitivity to detrimental effects shown in the multicenter Italian arm of the IBIS study.

In conclusion, IARC evalutation [22] of positive and negative effects by TAM in different target organs is emblematic: in humans, TAM is carcinogenic for endometrium whereas it is capable of reducing the risk of contralateral breast carcinoma.

Submitted on invitation.
Accepted on 10 April 2006.

References

1. Fisher B, Costantino JP, Redmond CK, Fisher ER, Wickerham DL, Cronin WM. Endometrial cancer in tamoxifen-treated breast cancer patients: findings from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14. *J Natl Cancer Inst* 1994;86:527-37.
2. Colacci A. Introduzione alla chemioprevezione. In: Amadori D, Grilli S (Ed.). *Oncologia Genetica*. Gaggiano (MI): Poletto Editore; 2001. p. 123-9.
3. Grilli S. Environmental carcinogenesis: tumour development and chemoprevention. *Tumori* 2001;87:S3-5.
4. Commissione Consultiva Tossicologica Nazionale (CCTN) (Italian Toxicology Advisory Committee). Rapporto dell'attività svolta nel 1990. Rossi L, Mucci N (Ed.). *Tamoxifen*. Roma: Istituto Superiore di Sanità; 1991. (Serie Rapporti Interni 91/1). p. 323-9.
5. Costa A. Breast cancer chemoprevention. *Eur J Cancer* 1993;29A: 589-92.
6. Sargent LM, Dragan YP, Bahnub N, Wiley JE, Sattler CA, Schroeder P, Sattler GL, Jordan VC, Pitot HC. Tamoxifen induces hepatic aneuploidy and mitotic spindle disruption after a single *in vivo* administration to female Sprague-Dawley rats. *Cancer Res* 1994;54(13):3357-60.
7. Vancutsem PM, Lazarus P, Williams GM. Frequent and specific mutations of the rat p53 gene in hepatocarcinomas induced by tamoxifen. *Cancer Research* 1994;54(14):3864-7.
8. Zito R. Problems in breast cancer prevention and therapy by tamoxifen. *J Exp Clin Cancer Res* 1994;13:99-101.
9. Gasco M, Argusti A, Bonanni B, Decensi A. SERMs in chemoprevention of cancer. *Eur J Cancer* 2005;41(13):1980-9.
10. Beland FA, Marques MM, Gamboa da Costa G, Phillips DH. Tamoxifen-DNA adduct formation in human endometrium. *Chem Res Toxicol* 2005;18(10):1507-9; author reply 1509-11.
11. Bush TL, Helzlsouer KJ. Tamoxifen for the primary prevention of breast cancer: a review and critique of the concept and trial. *Epidemiologic Reviews* 1993;15:233-43.
12. Seachrist L. Restating the risk of tamoxifen. *Science* 1994;263: 910-1.
13. Ross PJ, Powles TJ. Results and implications of the Royal Marsden and other tamoxifen chemoprevention trials. *Clin Breast Cancer* 2001;2:33-6.

14. Colacci A. Chemioprevenzione nei gruppi a rischio. In: Amadori D, Grilli S (Ed.). *Oncologia Genetica*. Gaggiano (MI): Poletto Editore; 2001. p. 191-205.

15. Robertson JF. Selective oestrogen receptor modulators/new antioestrogen: a clinical perspective. *Cancer Treat Rev* 2004;30:695-706.

16. Smith RE, Good BC. Chemoprevention of breast cancer and the trials of National Surgical Adjuvant Breast and Bowel Projects and others. *Endocr Relat Cancer* 2003;10:347-57.

17. Jakesz R, Jonat W, Gnant M, Mittlboeck M, Greil R, Tausch C, Hilfrich J, Kwasny W, Menzel C, Samonigg H, Seifert M, Gademann G, Kaufmann M, Wolfgang J; ABCSG and the GABG. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. *Lancet* 2005;366:455-62.

18. Cuzick J. Aromatase inhibitors in prevention - data from the ATAC (arimidex, tamoxifen alone or in combination) trial and the design of IBIS-II (the second International Breast Cancer Intervention Study). *Recent Results Cancer Res* 2003;163:96-103.

19. Mokbel K. Risk-reducing strategies for breast cancer- a review of recent literature. *Int J Fertil Women Med* 2003;48:274-7.

20. Johansen AM. Breast cancer chemoprevention: a review of selective estrogen receptor modulators. *Clin J Oncol Nurs* 2005; 9:317-20.

21. Kramer B, Brown P. Should tamoxifen be used in breast cancer prevention? *Drug Saf* 2004;27:979-89.

22. IARC Monographs on the evaluation of carcinogenic risks to humans. Tamoxifen. In: *Some pharmaceutical drugs*. Lyon: International Agency for Research on Cancer; 1996. Vol. 66. p. 253-365.