European Journal of Pharmacology 764 (2015) 372–378

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Review

Rethinking tamoxifen in the management of melanoma: New answers for an old question

Mariana P.C. Ribeiro [a,b,*], Armanda E. Santos [a,b], José B.A. Custódio [a,b]

[a] Center for Neuroscience and Cell Biology, University of Coimbra, 3000-354 Coimbra, Portugal
[b] Laboratory of Biochemistry, Faculty of Pharmacy, University of Coimbra, 3000-548 Coimbra, Portugal

ARTICLE INFO

Article history:
Received 29 May 2015
Received in revised form
29 June 2015
Accepted 8 July 2015
Available online 9 July 2015

Keywords:
Melanoma
Tamoxifen metabolism
Endoxifen
Estrogen receptor α
G protein coupled estrogen receptor

ABSTRACT

The use of the antiestrogen tamoxifen in melanoma therapy is controversial due to the unsuccessful outcomes and a still rather unclarified mechanism of action. It seemed that the days of tamoxifen in malignant melanoma therapy were close to an end, but new evidence may challenge this fate. On one hand, it is now believed that metabolism is a major determinant of tamoxifen clinical outcomes in breast cancer patients, which is a variable that has yet to be tested in melanoma patients, since the tamoxifen active metabolite endoxifen demonstrated superior cytostatic activity over the parent drug in melanoma cells; on the other hand, new evidence has emerged regarding estrogen-mediated signaling in melanoma cells, including the methylation of the estrogen receptor-α gene promoter and the expression of the G protein coupled estrogen receptor. The expression of estrogen receptor-α and G protein coupled estrogen receptor, as well as the cytochrome P450 (CYP) 2D6 genotype, may be used as predictive biomarkers to select the patients that may respond to antiestrogens based on specific traits of their tumors. This review focused on these new evidences and how they may contribute to shed new light on this long-lasting controversy, as well as their possible implications for future investigations.

Contents

1. Introduction

Introduced in the clinical practice in 1977, tamoxifen remains the standard therapy for women with estrogen receptor-positive breast carcinoma and it is estimated that the lives of half a million women were spared by adjuvant therapy with tamoxifen (Jordan, 2008). Tamoxifen is also used in the preventive setting in women at high risk.

It is widely accepted that the pharmacological action of tamoxifen in breast cancer is mainly mediated by binding to estrogen receptor-α, a member of the nuclear receptor superfamily that plays a pivotal role in the regulation of estrogen-mediated gene expression. The estrogen receptor has two independent functional domains, the activator function 1 (AF-1), in the amino-terminal domain, and activator function 2 (AF-2), in the ligand-binding domain. Upon estradiol binding to the estrogen receptor, there is a conformational change that is followed by dimerization and

* Corresponding author. Present address: Departament de Ciencies Basiques, Facultat de Medicina i Ciencies de la Salut, Universitat Internacional de Catalunya, Barcelona, Catalunya, Spain.
E-mail address: marianaponte@msn.com (M.P.C. Ribeiro).

http://dx.doi.org/10.1016/j.ejphar.2015.07.023
0014-2999/

binding to estrogen response elements; these events will lead to transcription of estrogen-dependent gene expression (Pietras, 2006). Full agonism requires both AF-1 and AF-2 to be active; when tamoxifen binds to the estrogen receptors, the AF-2 is no longer functional, while the AF-1 remains active (Wakeling, 2000). The partial agonism attributed to AF-1 seems to account for the different effects promoted by tamoxifen on different tissues. Indeed, tamoxifen has a carcinogenic action on uterus and endometrium (Ault and Brandbury, 1998).

The demonstration that some estrogen receptor-negative breast cancers also respond to tamoxifen, raised the possibility of an antitumor mechanism independent of the estrogen receptors (Croxtall et al., 2004; Charlier et al., 1995). Some of the mechanisms reported for tamoxifen in estrogen receptor-negative cancer cells include the inhibition of protein kinase C signaling (Gundimeda et al., 1996; Gelmann, 1997; Matsuoka et al., 2009) and the inactivation of the insulin-like growth factor-1 receptor (Kanter-Lewensohn et al., 2000). Moreover, emerging evidences show that tamoxifen can also act through the G protein coupled estrogen receptor (formerly GPR30) to evoke antiproliferative effects (Ariazi et al., 2010; Chan et al., 2010), although the antitumor G protein coupled estrogen receptor-mediated signaling might be dependent on the tumor cell type.

Importantly, tamoxifen is extensively metabolized in the liver and its steady-state levels are highly variable (Ingle et al., 1999), suggesting that the dose of tamoxifen needs to be adjusted according to the patient (Ingle, 2008).

2. The use of tamoxifen in malignant melanoma therapy is an unsuccessful story

The influence of sex hormones in the development and progression of melanoma has been a controversial topic over the last decades, but the existence of gender differences seems to be undeniable, as demonstrated by recent studies conducted in large numbers of patients. In a population-based cohort study analyzing 11,774 melanoma cases extracted from the Munich Cancer Registry (Germany), localized melanomas in women had a lower propensity to metastasize and better survival when compared with men (Joosse et al., 2011). In a different study, which included 2,672 patients with stage I/II melanoma, women had advantage in overall survival, disease-specific survival, time to lymph node metastasis, and time to distant metastasis (Joosse et al., 2012). The female advantage regarding survival and relapse/progression-free survival in metastasized states III and IV was also reported (Joosse et al., 2013).

The growing evidence that estradiol may regulate melanoma progression relights the discussion whether there is a role for antiestrogens in melanoma therapy.

The effects of tamoxifen on ovarian cancer, malignant glioma, melanoma, as well as on hepatocellular, pancreatic, and renal cell carcinomas, were investigated in several clinical trials (Gelmann, 1996, 1997; Goldenberg and Froese, 1982). Although tamoxifen individually has provided extremely poor response rates (less than 10%) in melanoma clinical trials (Rümke et al., 1992; Toma et al., 1999), the synergistic effects reported when tamoxifen was combined with other agents, such as fotemustine (Fischel et al., 1994), cisplatin (Jones et al., 1997; McClay et al., 1993) and interferons (Lindner and Borden, 1997), have led to the investigation of the benefits of the inclusion of tamoxifen in combination regimens. However, while some trials provided encouraging results, others failed to show significant improvements in clinically relevant endpoints (Table 1).

In a systematic review and meta-analysis of six randomized controlled trials to assess the benefit of tamoxifen addition to various chemotherapy and biochemotherapy regimens, tamoxifen failed to improve the overall response rate, the complete response rate or the survival rate in metastatic disease (Lens et al., 2003). More recently, in a meta-analysis including nine randomized controlled trials, the inclusion of tamoxifen in systemic chemotherapy improved the overall and the partial response of patients with advanced melanoma, with female patients being more likely to respond (Beguerie et al., 2010). However, the incidence of hematologic toxicity was higher in the tamoxifen group, and there was no improvement in 1-year mortality (Beguerie et al., 2010).

Although the clinical trials performed up to now produced unsuccessful results, the knowledge regarding tamoxifen action mechanisms and metabolism has substantially increased and the experience gained in breast cancer patients may unravel new clues to solve this controversy.

3. The clinical efficacy of tamoxifen is limited by its metabolism

Tamoxifen is extensively metabolized in the liver (Kiyotani et al., 2012). The *N*-demethylation of tamoxifen, primarily catalyzed by cytochrome P450 (CYP) 3A4 and CYP3A5, produces the major metabolite of tamoxifen, *N*-desmethyltamoxifen, which is

Table 1
The table lists selected clinical trials on the use of tamoxifen individually or in combination with other agents in melanoma patients. Several clinical trials were performed to assess the benefits of the inclusion of tamoxifen in melanoma treatment, but unsuccessful results were obtained. TAM, tamoxifen.

	Disease	Inclusion of TAM	Reference
TAM + dacarbazine	Metastatic	Beneficial	Cocconi et al. (1992)
TAM + dacarbazine + cisplatine			Flaherty et al. (1996)
TAM + dacarbazine + cisplatin + carmustine	Advanced		Chiarion-Sileni et al. (2001)
TAM		No benefit	Rümke et al. (1992)
TAM + dacarbazine + cisplatin + carmustine			Creagan et al. (1999)
TAM + paclitaxel	Metastatic	Benefit unclear	Nathan et al. (2000)
TAM + dacarbazine + cisplatin + carmustine	Metastatic	No benefit	Lattanzi et al. (1995), McClay et al. (1989), and Rusthoven et al. (1996)
TAM + dacarbazine or + dacarbazine + interferon-α			Falkson et al. (1998)
TAM + dacarbazine + carboplatin			Agarwala et al. (1999)