Asian Oncology Research Journal

3(4): 55-70, 2020; Article no.AORJ.62890

Repurposing Bazedoxifene for Cancer Therapeutics: It is Much more than a SERM

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Author's contribution

The sole author designed, analysed, interpreted and prepared the manuscript.

Article Information

Editor(s):
(1) Dr. Bing Yan, Hainan Branch of PLA General Hospital, China.
Reviewers:
(1) Ahmed Mohammed Morsy, Assiut University, Egypt.
(2) Mohd Adzim Khalili Bin Rohin, Universiti Sultan Zainal Abidin (UniSZA), Malaysia.
Complete Peer review History: http://www.sdiarticle4.com/review-history/62890

Review Article

Received 18 September 2020
Accepted 23 November 2020
Published 11 December 2020

ABSTRACT

Bazedoxifene (BDF) is a selective estrogen receptor modulator (SERM) that has been approved by the FDA for the treatment of post-menopausal osteoporosis in association with conjugated estrogens. BDF shares many of the pharmacological effects of tamoxifen with the advantage of not being an ER agonist in uterus and decreasing the risk for endometrial carcinoma induced by tamoxifen.

Interestingly, BDF has shown anti-tumoral actions in tissues and tumors that are hormone-independent. This means that BDF is not only a SERM. The better known of these mechanisms are

1) Inhibition of the IL6-IL6R-GP130-STAT 3 axis (IL6: interleukin 6; IL6R: interleukin 6 receptor; GP130: glycoprotein 130; STAT3: Signal Transducers and Activators of Transcription-3.
2) Modulation of the Hippo-YAP pathway.
3) Inhibition of AOX1 (aldehyde oxidase 1)

The first two are neatly anti-tumoral. The third one is sort of controversial.

This review is focused on the non-hormonal anti-tumor mechanisms of BDF. Its repurposing for the treatment of malignancies, other than breast cancer, is analyzed.

Keywords: Bazedoxifene; SERM; interleukin 6; interleukin 6 receptor; GP130; STAT3; breast cancer.

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1. INTRODUCTION

At the end of the XIX century the Scottish surgeon George Beatson, based on the observation of the ovarian influence on the breast of animals, removed both ovaries in three patients with breast cancer. To his surprise all the three improved. He had no idea about hormones or estrogens [1], but unknowingly the first step in the relationship between estrogens and breast cancer started to be disclosed.

At the beginning of the 1980s a firm suspicion on the role of estrogen replacement therapy in breast cancer developed in the scientific community [2,3]. All the evidence showed that hormone replacement therapy in postmenopausal women increased the risk of breast cancer and that estrogen depletion could be an important mechanism for its treatment. Research was oriented towards the discovery of an anti-estrogen compound. Tamoxifen, not being the first, was found to be quite effective as an anti-estrogen in breast [4].

On October 2013 the Food and Drug Administration (FDA) approved bazedoxifene (Bazedoxifene CAS#198481-32-2). The FDA approved the new medication Duavee ®, comprised of Bazedoxifene (BDF) and conjugated estrogens as a preventive treatment for postmenopausal flushes and osteoporosis. BDF has been previously approved by the European Medicines Agency in 2009. The addition of BDF to the conjugated estrogens decreases excessive growth of the uterine mucosa, lowering uterine cancer risk due to estrogens. Leaving aside the conjugated estrogens, our analysis will be limited to BDF as a possible anticancer drug.

BDF is an indole derivative (Fig. 1) acting as a selective estrogen receptor modulator (SERM) and selective estrogen receptor degrader (SERD) with mixed agonist and antagonist actions on the estrogen receptor (ER) according to tissue specificity.

It has ER antagonistic effects on breast and uterus, while tamoxifen being an antagonist in breast is an agonist in uterus. BDF binds the estrogen receptors (ER) in responsive tissues, such as breast, endometrium, bone, and liver. BDF bound to ER translocates to the nucleus where it may act as an antagonist in breast and endometrium blocking the effects of estrogen-ER complex. It can also act as an agonist in liver, modifying lipid metabolism decreasing total and LDL cholesterol [5]. Effects on bone are mainly anti- resorption increasing mineral density. BDF's main pharmacological characteristic is its tissue specificity. It is an estrogen antagonist in some tissues and at the same time an agonist in others.

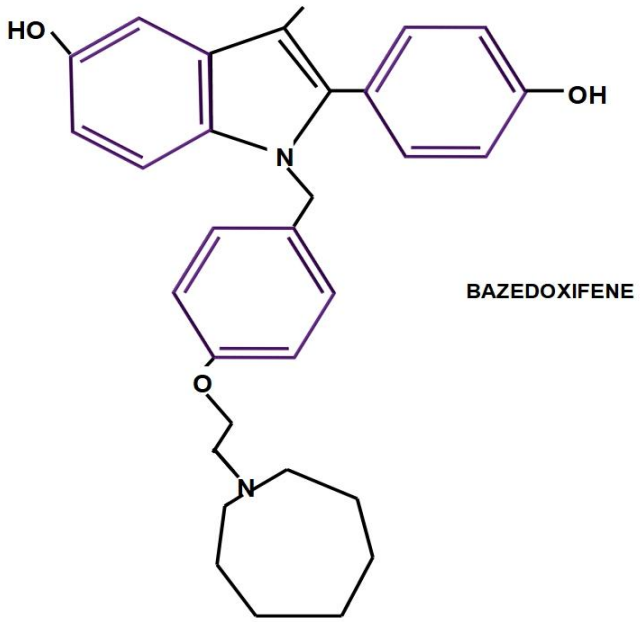

Fig. 1. Chemical structure of the hybrid SERM/SERD bazedoxifene

BDF is used in the following situations:

1) Prevention and/or treatment of breast cancer [6].
2) Prevention and/or treatment of post-menopausal osteoporosis [7,8,9,10].
3) Treatment of menopausal symptoms such as hot flashes (associated with conjugated estrogens) [11,12,13].

The objective of this review is to analyze BDF for the treatment of cancer in general, including but not exclusively breast cancer. The other two indications, namely osteoporosis and hot flashes will not be considered here. (Reviewed by Peng et al. [14], Banzal et al. [15], and Parish et al. [16])

2. NON-HORMONAL ANTICANCER ACTIONS OF BAZEDOXIFENE

The mechanism of action of bazedoxifene in non-hormonal cancer has not been fully cleared, but evidence has been accumulating in this sense. It is a SERM and a SERD, but acts also on hormone-independent breast cancer [17] showing that there must be other actions involved.

In the first place, as a SERM it has effects that are superior to that of tamoxifen rendering it useful in the treatment of tamoxifen-resistant breast cancer [18,19]. Resistance to tamoxifen is acquired through mutations of the estrogen receptor alpha (ERα). BDF has the ability to degrade these mutant forms of ERα [20], therefore it is also a SERD. These mutations are quite common after cancer treatment [21].

BDF potentiated anti-tumoral action of paclitaxel in breast cancer, increasing apoptosis, decreasing cell viability, migration and colony formation [22]. It was shown to be an inhibitor of triple negative breast cancer cells growth. This was accomplished by an independent activity from ER through inhibition of the IL6-GP130 pathway [23,24,25]. The inhibition of this axis has an anticancer role in breast cancer and also in other hormonal-independent tumors.

Three BDF effects related with non-hormonal cancers were clearly identified:

4) Inhibition of the IL6-IL6R-GP130-STAT 3 axis (IL6: interleukin 6; IL6R: interleukin 6 receptor; GP130: glycoprotein 130; STAT3: Signal Transducers and Activators of Transcription-3.
5) Modulation of the Hippo-YAP pathway.
6) Inhibition of AOX1 (aldehyde oxydase 1)

2.1 Inhibition of the IL6-IL6R-GP130-STAT 3 Axis

The mechanisms involved in this pathway are:

1) binding of IL-6 to the IL-6 receptor (IL-6R);
2) thus inducing activation of the receptor with
3) homodimerization and recruitment of glycoprotein 130 (GP130);
4) while IL-6 R is not a signaling molecule, GP130 is the actual signaling glycoprotein [26];
5) this pro-tumoral signaling plays a role in growth and metastasis of breast cancer cells [27] and other tumors.

STAT3 is one of the main downstream protein targets, through the JAK-STAT axis. Fig. 2.

As shown in Fig. 2 there are many pro-tumoral pathways initiated by the signaling of IL6-IL6R besides the JAK-STAT pathway. Therefore, IL6-IL6R-GP130 can be considered an oncogenic cytokine hub.

Fig. 2 shows membrane-bound IL6R activation and signaling. However, there is a second mechanism involved that seems to be at least, or more important than membrane-bound IL6R activation. This is the activation of the soluble form of IL6R.

Soluble IL6R (sIL6R) has two origins [28]:

a) alternative splicing of the IL6R primary transcript [29];
b) limited proteolysis and shedding of the membrane bound IL6R [30].

Uniprot [31] says that “the restricted expression of the IL6R limits classic IL6 signaling to only a few tissues such as the liver and some cells of the immune system. Whereas the binding of IL6 and soluble IL6R to IL6ST stimulates 'trans-signaling' ” [32]. It is GP130 that explains the pleiotropic effects of cytokines like IL-6. BOX1. This explains how IL6 is able to produce effects in cells lacking IL-6R. This process has been called transignaling. The common intermediate signaling molecule in both cases is GP130. Blocking of IL-6 impedes both mechanisms leading to GP130 signaling, namely, classic membrane IL-6R binding and transignaling.

BOX 1: TWO MECHANISMS OF IL-6 ACTIVITY
1) Binding of membrane bound IL-6R and signaling through GP130 2) Binding to soluble IL-6R and signaling through membrane bound GP130

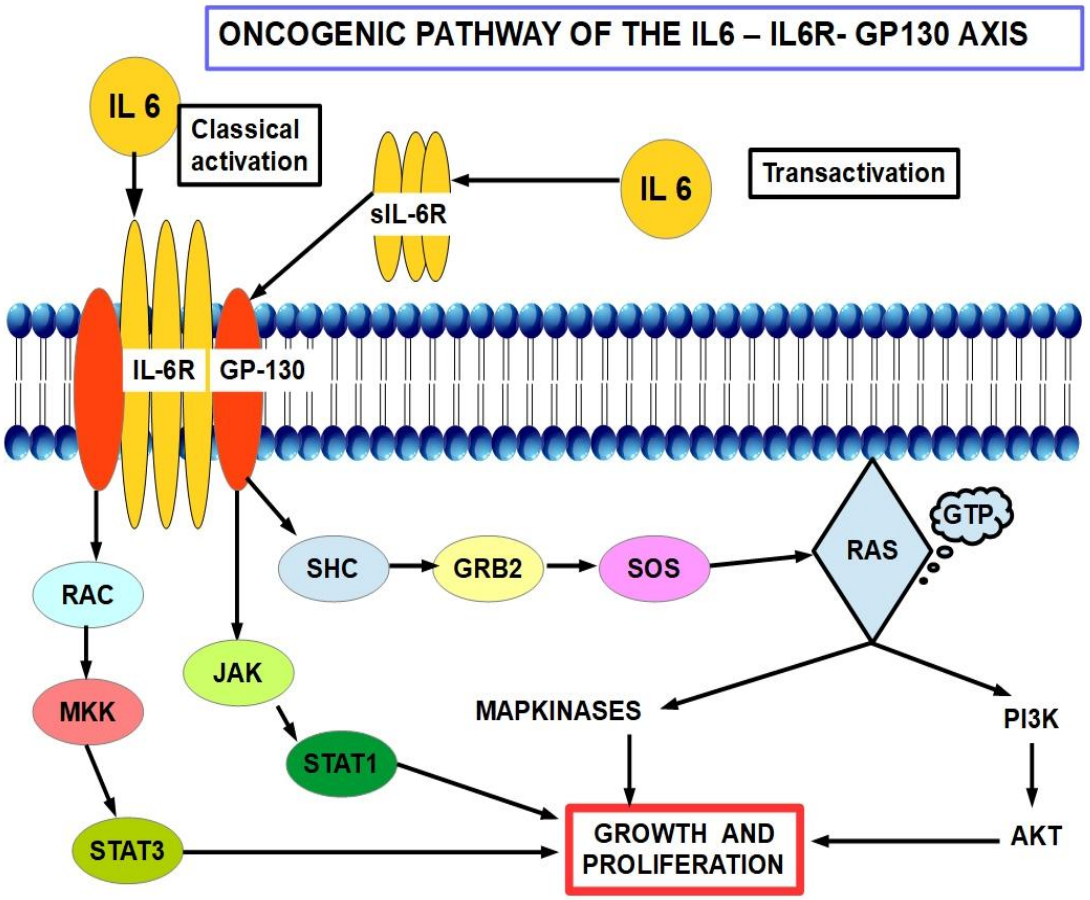

Fig. 2. Oncogenic pathways of the IL6-IL6R-GP130-STAT3 axis at the membrane level. This figure is based on references [33,34,35,36,37,38,39,40,41,42], IL-6 is a cytokine that affects the immune system, inflammation, hematopoiesis, and oncogenesis. It regulates cell growth, gene activation, proliferation, survival, and differentiation. Signaling of IL6 requires the IL6 receptor and GP (Glycoprotein) 130, Binding of IL-6 to its receptor initiates cellular events including activation of JAK (Janus Kinase) and Ras-mediated signaling. Activated JAK phosphorylates and activates STAT transcription factors, particularly STAT3. Activated STAT3 translocates into the nucleus to activate transcription of genes containing STAT3 response elements. STAT3 is essential for GP130-mediated cell survival and G1 to S cell-cycle-transition signals. STAT3 was found to be constitutively activated in many tumors [43]. The Ras-mediated pathway activates MAP kinases downstream. Also PI3K-AKT axis is activated. (PI3K: phosphoinositol 3 kinase; AKT: protein kinase B)

The IL6-IL6R-GP130-STAT3 axis has been described by Chen et al. [44] as a pro-tumoral "vicious" forward cycle driving the tumor, in which IL6 induces STAT3 expression and STAT3 increases IL6. BOX 2

BOX 2
IL6-→IL6R-→GP130-→STAT3----→IL6….

This pathway has been found to be active in pancreatic cancer and BDF has been proposed as part of the treatment of this cancer, where it seems to down-regulate the IL6/PG130/STAT3 pathway [45,46,47,48]. In pancreatic cancer, the evidence indicates that the anti-cancer mechanism is independent of the hormonal effects of BDF on the ERα. The IL6-GP130-STAT3 signaling axis seems to be an important

tumor driver in many cancers [49,50,51,52,53], including pancreatic cancer. BDF has the ability to disrupt this axis by interfering the IL6R-GP130 relationship, thus blocking GP130 signaling.

This axis is also operative in other tumors where BDF decreased their growth, such as rhabdomyosarcoma [54], head and neck cancer [55], triple negative breast cancer [56], gastrointestinal cancer [57] including colon cancer [58] and gastric cancer [59], medulloblastoma [60], osteosarcoma [61], and hepatocellular carcinoma [62], among others.

Down-regulation of the IL-6R-GP130 signaling has shown synergy with classical oncological treatments such as 5-fluorouracyl in colon cancer [63], paclitaxel in breast cancer, and targeted treatments like lapatinib in breast cancer [64], and palbociclib also in metastatic breast cancer [65].

The persistence of high GP130-STAT signaling in human rhabdomyosarcoma was found to be involved in resistance to cisplatin, doxorubicin and MEK inhibitors [66]. BDF suppressed the resistance.

There is no evidence of BDF actions on human lung cancer. However, in a Drosophila lung tumor model BDF showed anti-tumor properties and synergism with afatinib [67].

2.2 Modulation of the Hippo-yap Pathway

Hippo is a protein kinase that controls growth, proliferation and apoptosis through a phosphorylation cascade that inactivates Yes-associated protein (YAP). Mutations of Hippo produce a loss of control of organs growth/size through the unrestricted activity of YAP [68].

There is evidence of its important oncogenic effects in Ewing sarcoma [69], glioblastoma [70], cervix cancer [71], among others. In glioblastoma BDF had the ability to penetrate the blood brain barrier and showed synergistic anti-tumoral effects with paclitaxel. Yap (yes-associated transcription factor coactivator) signaling promotes migration and progression in glioblastoma [72] and in malignant tumors in general [73]. It has not been clearly established the level at which BDF interferes with the Hippo-Yap pathway.

2.3 Inhibition of AOX1

Aldehyde oxidase 1 is an enzyme that intervenes in the detoxification process of aldehydes and the production of ROS (reactive oxygen species) such as hydrogen peroxide (H2O2) and superoxide [74]. It is mainly expressed in liver, kidney, adrenal gland, and to a lesser extent in ovary, testis, prostate and pancreas.

Chen et al. found that BDF, but also some other SERMS had an inhibitory effect on AOX1 [75].

AOX1 is involved in the development of colon cancer [76]. However, the role of AOX1 in cancer is controversial. For example, down-regulated expression of AOX1 promoted bladder cancer progression [77].

2.4 Reduction of VEGF, VEGFR2 and COX2

Hou et al. [78] found in a rat endometriosis model that BDF had the ability to reduce proteins related with angiogenesis such as VEGF, VEGFR2 and COX2. There is no proof that this happens also in human tumors. These effects may be hormone-dependent, however, the authors also found concomitantly decreased levels of IL1, IL2, IL6, and TNFα. Thus, the reduction of VEGF, VEGFR2 and COX2 can be a consequence of the IL6 pathway inhibition.

2.5 Aryl Hydrocarbon Receptor Activation

BDF is able to activate the aryl hydrocarbon receptor (AHR) in breast cancer cells whether ERα positive or negative [79]. AHR is a cytosolic transcription factor regulating stem cell maintenance and cell differentiation and is activated by different natural and synthetic ligands. Ligand-activation of AHR allows its translocation into the nucleus where it regulates specific genes, many of them related with metabolism [80]. AHR is involved in the regulation of many pathways related with proliferation, cell motility and differentiation [81]. AHR participates in different stages of carcinogenesis and its progression [82]. The results of AHR activation is a controversial issue, because it produces pro- and anti-tumoral effects. And to further complicate the issue, effects may differ according to the activating ligand. A group of substances, such as MCDF (6-methyl-1,3,8-trichlorodibenzo-*p*-dioxin), are at the same time AHR agonists and exert antiestrogenic activity [83]. BDF probably

belongs to this group where the AHR agonism is associated with antiestrogenic effects.

3. RENAL CELL CARCINOMA

There are no publications about the use of BDF in renal cell carcinoma (RCC). In male rats, the prolonged BDF administration caused renal tubular tumors [84]. However, BDF was not found to be genotoxic [85]. A high serum level of IL6 was predictive of recurrence in RCC [86].

4. DISCUSSION

Bazedoxifene is a SERM and a SERD that is useful for the treatment of breast cancer through its blocking of the ERα. Besides this hormonal action it showed other anti-cancer non hormone-dependent effects.

The IL-6/GP130/STAT3 signaling pathway is essential for the survival and progression of some cancers. Furthermore, a well known oncoprotein like STAT3 is activated by this signaling pathway in such a manner that a forward loop between IL-6-STAT3-IL6 has been found. We may say that these tumors are IL-6 dependent and IL6 driven. In these kind of tumors BDF has shown efficacy as an associated drug to classical chemotherapies or targeted treatments.

BDF is an effective inhibitor of the IL6 signaling pathway. Therefore, its usefulness goes beyond hormone-dependent tumors.

BDF is not a stand alone drug. It needs to be associated with other chemotherapeutic drugs. It also showed ability to reverse multiple drug resistance in heavily treated cases.

However, there are no ongoing experimental protocols with this drug in cancer treatment other than breast. (Clinicaltrials.gov has 48 registered studies as of October 2020. Most of them are for menopausal symptoms and osteoporosis. Six studies are for breast cancer. There are no studies for other type of cancers).

In patients with high serum IL-6 levels a correlation was found between clinico-pathological features, survival and IL-6 level. This has been confirmed in many types of malignant tumors, such as prostate [87,88,89], colorectal [90,91,92], lung [93], breast [94], gastric [95], ovary [96], head and neck [97], among others.

Does this mean that these tumors are IL-6/GP130/STAT3 driven?

Probably not, in many cases. It is not possible to determine if the serum IL-6 increase is causally related with the tumor [98] Furthermore, it can be increased by hypoxia, whether generalized or at the tumor level [99,100,101,102]. However, it is evident that in these increased serum IL-6 tumors the cytokine is playing an important role and it is not an innocent bystander.

IL-6 increase at the tumor level, whether cause or consequence needs to be taken care of because it has notorious pro-tumor activities besides the IL-6/IL-6R/GP130/STAT3 pathway. Some of these pro-tumoral effects are:

1) promotion of epithelial-mesenchymal transition [103,104];
2) producing immuno evasion through phosphorylation of programmed death ligand-1 (PDL-1) [105];
3) promotion of migration, invasion and metastasis [106,107,108];
4) contribution to chemoresistance [109,110];
5) promotion of stem cell like properties [111,112];
6) contribution to cancer progression through the osteopontin-NF-kB pathway [113];
7) inducing an inflammatory pro-tumoral environment [114,115];
8) stimulating angiogenesis [116] by
   a) increasing vascular endothelial growth factor (VEGF) [117,118],
   b) stimulating circulating blood-derived progenitor endothelial vascular cells[119], and
   c) basic fibroblast growth factor (bFGF) induction [120];
9) contribution to cancer cachexia [121,122,123];
10) promotion of myeloid-derived suppressor cells [124];
11) promotion of the cyclooxygenase 2 (COX2)/prostaglandin E2 (PGE2) /β-catenin signaling [125].

BDF on the other hand is a non-toxic drug that can be added to any treatment protocol without enhancing patients toxicity with the added value of its synergy with classical or targeted treatments. Importantly, BDF administered at usual doses lacks toxicity [126,127,128, 129,130,131].

The lack of clinical trials on this matter should change and BDF should come into the

therapeutic perspective once its benefits are further confirmed with well planned prospective clinical trials.

5. CONCLUSIONS

There are a group of tumors in which the IL-6/GP130/STAT3 is a driver pathway. In these tumors the association of the non-toxic SERM BDF should improve treatment results. The difficulty lies in determining when a tumor is driven by this pathway. At this stage of our knowledge the serum IL-6 level is not a proof in this sense. Probably, those tumors with normal serum IL-6 levels are not driven by the IL-6 pathway. However, the tumors that express high IL-6, GP130 and STAT3 in the specimen should be considered for associating BDF to the treatment protocol. There is evidence that BDF can be beneficial also in tumors that are not driven by the IL-6/GP130/STAT3.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sdiarticle4.com/review-history/62890