Biomedicine & Pharmacotherapy 101 (2018) 458–477

Contents lists available at ScienceDirect

Biomedicine & Pharmacotherapy

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

Chemotherapeutic agents for the treatment of metastatic breast cancer: An update

Mariam Abotaleb[a,1], Peter Kubatka[b,c,1], Martin Caprnda[d,1], Elizabeth Varghese[a], Barbora Zolakova[c], Pavol Zubor[e], Radka Opatrilova[f], Peter Kruzliak[g,h,*], Patrik Stefanicka[i,**], Dietrich Büsselberg[a,***]

[a] Weill Cornell Medicine in Qatar, Qatar Foundation-Education City, Doha, Qatar
[b] Department of Medical Biology, Jessenius Faculty of Medicine, Comenius University in Bratislava, Martin, Slovakia
[c] Department of Experimental Carcinogenesis, Division of Oncology, Biomedical Center Martin, Jessenius Faculty of Medicine, Comenius University in Bratislava, Martin, Slovakia
[d] 1st Department of Internal Medicine, Medical Faculty, Comenius University in Bratislava, Bratislava, Slovakia
[e] Clinic of Gynecology and Obsterics, Jessenius Faculty of Medicine, Comenius University in Bratislava, Martin, Slovakia
[f] Department of Chemical Drugs, Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences, Brno, Czech Republic
[g] Department of Internal Medicine, Brothers of Mercy Hospital, Brno, Czech Republic
[h] 2nd Department of Surgery, Faculty of Medicine, Masaryk University and St. Anne´s University Hospital, Brno, Czech Republic
[i] Department of Otorhinolaryngology, Head and Neck Surgery, Faculty of Medicine, Comenius University and University Hospital, Antolska 11, 851 07, Bratislava, Slovakia

ARTICLE INFO

Keywords:
Metastatic breast cancer
Chemotherapy
Efficacy
Toxicity
Resistance
Antimetabolites
Immunologic therapy
Hormonal/endocrine therapy
DNA alkylating agents
Ion modulators
Antimitotic agents

ABSTRACT

Breast cancer is the second greatest cause of death among women worldwide; it comprises a group of heterogeneous diseases that evolves due to uncontrolled cellular growth and differentiation and the loss of normal programmed cell death. There are different molecular sub-types of breast cancer; therefore, various options are selected for treatment of different forms of metastatic breast cancer. However, the use of chemotherapeutic drugs is usually accompanied by deleterious side effects and the development of drug resistance when applied for a longer period. This review offers a classification of these chemotherapeutic agents according to their modes of action and therefore improves the understanding of molecular targets that are affected during treatment. Overall, it will allow the clinician to identify more specific targets to increase the effectiveness of a drug and to reduce general toxicity, resistance and other side effects.

1. Introduction

Breast cancer (BC) is the most widespread type of cancer amongst women, comprising 26% of cancer cases and ranking as the second greatest cause of female mortality worldwide. Generally, the risk of BC increases with age, but it also has a genetic component, as its development is frequently induced by mutations of genes that control cellular differentiation and growth [1,2]. BC treatment is a great challenge, as it is a heterogeneous disease compromising different subtypes with diverse but specific properties, both clinically and biologically. Therefore, identification of BC subtypes is important to select the best therapeutic strategy [3]. BC is classified by stage, histology, grade differentiation and, most importantly, at the molecular level by the presence or absence of a hormonal receptor (HR+/−)

Abbreviations: 5-FU, 5-Fluorouracil; AI, aromatase inhibitor; BC, breast cancer; CDK, cyclin-dependent kinase; DHF, dihydrofolate; DHFR, dihydrofolate reductase; ER, estrogen receptor; FSH, follicle stimulating hormone; FDA, Food & Drug Administration; GnRH, gonadotrophin releasing hormone; HR, hormone receptor; HER, human epidermal growth receptor; IGF, insulin-like growth factor; LH, luteinizing hormone; MBC, metastatic breast cancer; PR, progesterone receptor; THF, tetrahydrofolate; TNBC, triple negative breast cancer

* Corresponding author at: Department of Chemical Drugs, Faculty of Pharmacy, University of Veterinary and Pharmaceutical Sciences, Palackeho tr. 1/1946, 612 42 Brno, Czech Republic.
** Corresponding author at: Department of Otorhinolaryngology, Head and Neck Surgery, Faculty of Medicine, Comenius University and University Hospital, Antolska 11, 851 07 Bratislava, Slovakia. Tel.: +420 26867 2052.
*** Corresponding author at: Weill Cornell Medicine in Qatar, Qatar Foundation-Education City, POB 24144 Doha, Qatar.
E-mail addresses: peter.kruzliak@muni.cz (P. Kruzliak), patrikstefanicka@yahoo.com (P. Stefanicka), dib2015@qatar-med.cornell.edu (D. Büsselberg).
[1] Co-first/equal authorship.

https://doi.org/10.1016/j.biopha.2018.02.108
Received 8 August 2017; Received in revised form 22 February 2018; Accepted 23 February 2018

5progesterone receptors, and the growth of the cancer correlates to these hormones [3–5].

HR+ is additionally classified into subtypes according to the genetic expression of human epidermal growth receptor 2 (HER 2). Luminal A is prevalent among 23% of BC patients and has mostly a good prognosis. It is classified as hormonal positive and does not express HER2 (HR+/HER 2−). Furthermore, it lacks the cell proliferation protein Ki67 [3,5]. Luminal B is the most prevalent type, constituting 52.8% of BC cases. In contrast to luminal A, it expresses the Ki67 protein and is further divided by the presence or absence of HER2 (HER2+/-). Its prognosis is less positive compared to Luminal A [3]. HR- subtypes lack estrogen and progesterone receptors and are also classified based on the presence of (HER 2); HER is either absent or enriched. For the latter case, which compromises 11–12% of this subgroup, the prognosis is poor. Basal-like cancer lacks the HER 2 receptors. It contributes 12–14% of BC subtypes, 90% of which are triple-negative (TNBC). This is the most aggressive subtype [3]. Finally, the unclassified normal-like BC types express estrogen and progesterone receptors but lack the HER2 receptor and the Ki67 protein. They have an intermediate prognosis, with 7.8% prevalence [3,5,6]. There are various treatment options for BC, including surgical removal of affected tissue, radiotherapeutic regimens and chemotherapeutic treatment.

Metastatic breast cancer (MBC) is a serious health problem worldwide, presenting mostly together with bone metastases as the most common site of disease recurrence. Metastases secondary to BC negatively impact patient survival and quality of life. Moreover, the clinical complications of MBC, i.e. solid organ and bone metastases, are associated with significant economic costs to the individual, the health care system and society as a whole, and they require long-term multidisciplinary health care (radiologists, oncologists, senologists, physicians, pathologists, etc.). The molecular mechanisms involved in metastasis, colonization and proliferation of BC cells are complex and involve crosstalk between BC cells and the metastatic site-specific microenvironment, supporting the current interpretation of the "Seed and Soil" theory of metastasis, which proposes that pre-metastatic niches are formed by primary tumors [5]. The ability of MBC cells to hijack normal biological processes in affected organs and genomic alterations in clonal metastatic cells different to the primary tumor is a key driver of relapse, potentiating the emergency to find the best neo/adjuvant treatment in primary or secondary management of MBC (Fig. 1).

1.1. Aim of the review

The focus of this article is an up to date review of the chemotherapeutic agents used in the treatment of MBC regarding their mechanism of action, efficacy, resistance and undesirable side effects. Chemotherapeutic drugs are discussed according to their mode of action (separated in the upcoming chapters as): antimetabolites, immunologic therapy, endocrine therapy, DNA alkylating agents, metal ions and antimitotic agents (Fig. 2).

1.2. Source of data

Data from the available biomedical literature were reviewed and pooled to evaluate metastatic breast cancer treatment regarding their mechanisms, resistance, clinical usage and toxicity. Relevant studies published in the literature were retrieved by the use of the following terms as either a keyword or a MeSH (medical subject heading) term in searches of the PubMed (US National Library of Medicine National Institutes of Health) bibliographic database: metastatic breast cancer, chemotherapy, trial, efficacy, toxicity, side effects, resistance, antimetabolites, immunologic therapy, hormonal/endocrine therapy, DNA alkylating agents, ion modulators, antimitotic agents. We focused on the most recent clinical data.

2. Antimetabolites

Antimetabolite agents interact with vital intracellular enzymes, leading to their inactivation or to the production of fraudulent products incapable of normal intracellular function. Their structures resemble analogues of normal purines and pyrimidines, or they resemble normal substances that are vital for cellular function. Some antimetabolites are active as intact drugs, and others require biotransformation into active agents. Although many of these agents act at different sites in biosynthetic pathways, they appear to exert their antitumor activity by disrupting functions crucial to the viability of the cell. These effects are usually more disruptive to actively proliferating cells; thus, antimetabolites are classed in general as cell cycle-specific agents. Antitumor antimetabolites are classified on the basis of the different enzymes they are targeting. Suppressors of enzyme activity include dehydrogenase inhibitors, nucleoside inhibitors, topoisomerase inhibitors and kinase inhibitors [7,8].

2.1. Dehydrogenase inhibitors

Methotrexate (MTX) (Fig. 3a) is a small antimetabolite molecule which acts synergistically with 5-FU. It is used for the treatment of a wide variety of cancers [7]. It is a competitive inhibitor for folate, as it prevents the enzymatic activity of dihydrofolate reductase (DHFR), which is the enzyme responsible for catalyzing the conversion of dihydrofolate (DHF) into tetrahydrofolate (THF). This leads to an accumulation of folates, which are required during purine synthesis, and

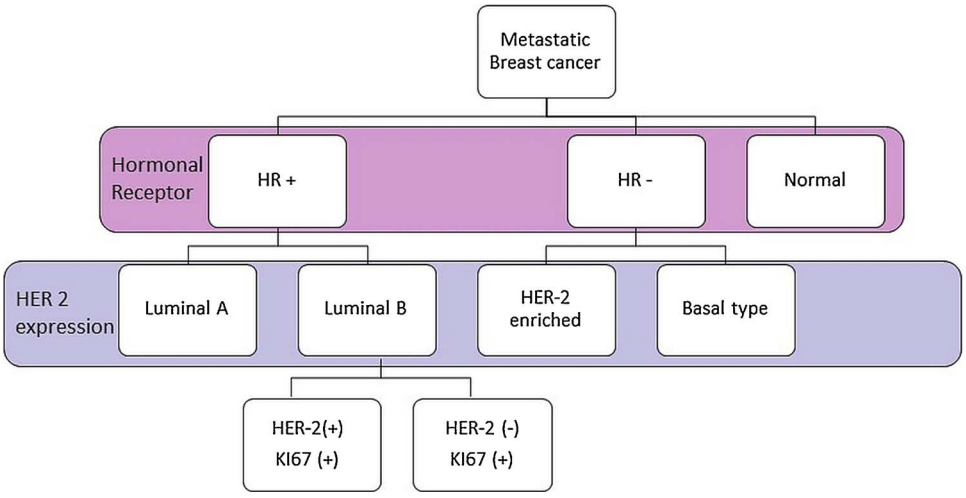

Fig. 1. Classification of breast cancer subtypes according to their hormonal receptor status to HR+, HR− and normal and according HER 2 expressions into luminal A, luminal B, HER2 enriched and basal. Breast cancer is composed of multiple subtypes with distinct morphologies and clinical implications. Molecular pathogenesis studies demonstrate that breast cancer as a heterogeneous disease is manifested with variable molecular underpinnings that modulate therapeutic responses, disease-free survival intervals and long-term survival. The precise characterization of breast cancer subtypes has facilitated targeted management strategies, advanced treatments and symptomatic care for oncological patients.