

Review

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Review

Multidrug Resistant Breast Cancer Management in Sub-Saharan Africa: Challenges, Pharmacological Strategies and Recommendations

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ABSTRACT: This article describes the challenges, pharmacological strategies, and recommendations for managing multidrug-resistant breast cancer in Sub-Saharan Africa (SSA). By examining the current breast cancer treatment landscape, region-specific challenges, and promising pharmacological interventions, the objective is to bring to light the insufficient research on breast cancer and its multidrug resistance in this part of the world and guide healthcare professionals, policymakers, and researchers in developing evidence-based strategies for improved breast cancer care in SSA. Breast cancer is the leading cause of cancer morbidity in SSA, necessitating continuous advancements in its management. This overview explores the evolution of breast cancer treatment, including surgery, targeted therapy, immunotherapy, radiotherapy, and chemotherapy. Despite these advancements, multidrug resistance poses a significant challenge, impacting treatment efficacy and patient outcomes. The article provides insights into various breast cancer treatment modalities, emphasizing surgery, targeted therapy, immunotherapy, radiotherapy, and chemotherapy. Each approach is discussed in detail, highlighting its significance in managing breast cancer. The effectiveness of these treatments is contingent on timely diagnosis and intervention. Multidrug resistance is examined as a critical obstacle in breast cancer treatment, elucidating its impact on treatment failure and patient outcomes. Mechanisms such as the efflux system, enhanced DNA repair, apoptosis inhibition, alterations in drug targets, and the tumor microenvironment contribute to multidrug resistance, emphasizing the need for a multifaceted understanding. The unique challenges faced in SSA regarding multidrug-resistant breast cancer are delineated. These include the lack of comprehensive data, late presentation and diagnosis, poor genomic studies, limited access to specialized care, financial constraints, inadequate infrastructure, and psychosocial support issues. Addressing these challenges is crucial for devising effective strategies. In response to multidrug resistance, the article discusses contemporary treatment strategies such as P-glycoprotein inhibitors, combined chemotherapy, and immunotherapy. Notable advancements, including the use of Tarividar and synergistic effects of combined chemotherapy, are highlighted, presenting promising avenues for overcoming resistance. The article proposes recommendations to enhance breast cancer management in SSA, encompassing strengthening primary healthcare services, creating specialized oncology facilities and long-term monitoring and data collection. Breast cancer management in SSA is multifaceted, marked by challenges and evolving solutions. Multidrug resistance remains a significant hurdle, demanding a holistic approach. Promising advancements in pharmacological interventions offer hope, while comprehensive recommendations serve as a roadmap for progress. By implementing these strategies, SSA can substantially improve multidrug-resistant breast cancer care and overall patient well-being.

OBJECTIVE

The primary aim is to comprehensively delineate the challenges, pharmacological strategies, and recommendations for the management of multidrug-resistant breast cancer in Sub-Saharan Africa. By examining the current landscape of breast cancer treatment, elucidating the challenges specific to the region, particularly the insufficient research on breast cancer and its multidrug resistance in this part of the world and exploring promising pharmacological interventions, we aim to provide insights that can guide healthcare professionals, policymakers, and researchers toward evidence-based strategies for improved breast cancer care in SSA.

INTRODUCTION

Breast cancer is the most common cancer in women, in 2022, there were 2.3million women diagnosed with breast cancer and 685,000 deaths globally (1). Breast cancer is the leading cause of cancer morbidity and the second highest number of mortalities from cancer in sub-Saharan Africa (SSA) (2). Over the last four decades there has been massive improvement in the management of breast cancer (3). These improvements are associated with introduction of enhanced screening methods and the integration chemotherapeutic drugs. (4)

OVERVIEW OF BREAST CANCER TREATMENT.

1. Surgery- Surgery (or resection) most often includes the removal of tissue from the body. The option of surgeries comprises of modified radical mastectomy and breast conserving surgeries like lumpectomy, choice is based on the extent of the disease, surgery also has a place in the diagnosis in the form of biopsies and axillary clearance. (5)
2. Targeted Therapy: Targeted therapy involves drugs or other substances that specifically target molecular pathways or molecules involved in cancer cell growth and survival. It is designed to be more precise and selective in its action compared to traditional chemotherapy. A very important example is HER2-targeted therapies like trastuzumab which have revolutionized outcomes for HER2-positive breast cancer (6). Hormone receptor-positive breast cancers can also benefit from endocrine therapies such as tamoxifen (7).
3. Immunotherapy: Immunotherapy is a type of treatment that stimulates the body's immune system to recognize and attack cancer cells. One notable example is the use of immune checkpoint inhibitors, such as pembrolizumab, which targets the PD-1/PD-L1 pathway (8)
4. Radiotherapy- Radiotherapy is a vital component of breast cancer treatment, used post-surgery to eliminate residual cancer cells and reduce recurrence risks. It employs high-energy rays, delivered externally or through implants, to target cancer cells while minimizing damage to healthy tissue. Advanced techniques like IMRT and proton therapy enable precise, targeted treatment. When combined with chemotherapy or hormone therapy, radiotherapy's effectiveness is further enhanced. While it may lead to temporary side effects, modern approaches and supportive care measures ensure a better quality of life for patients undergoing treatment. (9)
5. Chemotherapy- These are cytotoxic drugs that acts systematically to kill cancer cells, the mechanism of action of each drug varies. (10)

Classes of chemotherapy and their common side effects (11)

- Alkylating Agents: These drugs form unstable alkyl groups that react with proteins and nucleic acids, inhibiting DNA replication and transcription. Examples include cyclophosphamide, and cisplatin. They can lead to myelosuppression, mucositis, neurotoxicity, and other long-term toxicities.
- Antimetabolites: They inhibit DNA replication. Examples include azacitidine, cytarabine, and methotrexate. They can cause myelosuppression, mucositis, and other toxicities.
- Antimicrotubular Agents: These drugs disrupt cellular function and replication. Examples include doxorubicin, etoposide, and paclitaxel. They may lead to myelosuppression, cardiotoxicity, diarrhea, and other toxicities.
- Antibiotics: These agents inhibit RNA and DNA synthesis. Examples include actinomycin D and bleomycin. Bleomycin also causes DNA breaks. They can result in cumulative pulmonary toxicity and hyperpigmentation.

Chemotherapy can be two forms (10)

- Neoadjuvant therapy: This type of therapy aims to debulk, shrink, or downstage tumors to make them more operable.
- Adjuvant therapy: This involves the administration of a chemotherapeutic drug after debulking surgery to further clear any remaining tumor cells.

The response of cancer to chemotherapeutic agents can be monitored using radiological imaging techniques like Fluorodeoxyglucose positron emission tomography and computed tomography that measures the activity of the cancer cell and the size respectively. (12,13). The ongoing challenge to management of breast cancer with chemotherapy is the development of resistance in the cancer cells

to chemotherapeutic drugs, the cause of the resistance can be newly developed with time or gained over time by the cancer cells (14).

MULTIDRUG RESISTANCE

Multidrug resistance in breast cancer refers to the phenomenon where cancer cells acquire resistance to multiple chemotherapy drugs, spanning various classes, thereby diminishing their responsiveness to treatment causing treatment failure (15). While chemotherapy has significantly improved outcomes for breast cancer patients, the challenge of multidrug resistance has been gradually diminishing the positive impact of this treatment. Research suggests that multidrug resistance can contribute to a substantial proportion of treatment failures, and it has been estimated to be a factor in a significant percentage of breast cancer-related fatalities, often cited as around 90%. This figure may vary based on the specific patient population, treatment protocols, and geographic regions. (16). Surprisingly, despite its increasing impact in clinical practice, there is a noticeable absence of comprehensive and dependable statistics concerning this crucial aspect of breast cancer in Sub-Saharan Africa from readily accessible online sources.

The heterogeneous nature of breast tumors has emerged as a pivotal factor in the development of multidrug resistance. Recent studies have identified 10 distinct subtypes (17), each requiring a tailored treatment approach. Understanding this diversity is crucial in devising effective therapeutic strategies. The development of multidrug resistance can be elucidated by multiple mechanisms.

MECHANISM OF MULTIDRUG RESISTANCE OF CANCER CELLS

1. Efflux system- Chemotherapy resistance often stems from increased drug efflux within cells, primarily facilitated by ATP-binding cassette (ABC) transporters. These transporters, categorized into seven subfamilies, include ABCB1, ABCC1, and ABCG2, which are specifically linked to multidrug resistance (MDR)(18). Overexpression of ABCB1, also known as P-glycoprotein, is common in various cancers, contributing to chemoresistance (19). Epigenetic factors, like CpG island hypermethylation, can influence ABCB1 expression (20). Additionally, ABCG2 plays a critical role in breast cancer therapy resistance and serves as a marker for cancer stem cells in triple-negative breast cancer. (21)
2. Enhanced cell DNA repairs- The DNA damage response (DDR) operates as a cascade of signals. Upon DNA damage, the sensor molecular system is activated, transmitting signals upstream to initiate DNA damage repair [22]. In the context of neoadjuvant chemotherapy drugs, which induce direct or indirect DNA damage, the DNA damage repair mechanism can counteract the drug-induced damage, leading to the development of drug resistance. Targeting key elements in this response, like PARP 1 mediated nucleotide excision repair (NER) [23], and PARP-1 inhibitors have been used in the treatment of breast cancer patients in clinical applications [24]; therefore, when using neoadjuvant chemotherapy drugs that directly or indirectly target DNA damage leading to the development of drug resistance, PARP-1 inhibitors can be considered in combination therapy to enhance drug efficacy.
3. Apoptosis inhibition- Apoptosis is crucial for the pharmacological effects of neoadjuvant chemotherapeutic drugs in breast cancer cells [25]. Resistance to apoptosis, mediated by factors like NF- κ B and Bcl-2 overexpression, hinders drug sensitivity, contributing to neoadjuvant chemotherapy resistance [26]. Additionally, c-Flip overexpression prevents pro-caspase-8 activation, inhibiting apoptosis and fostering drug resistance [27,28].
4. Autophagy, a type II programmed cell death, often acts antagonistically to apoptosis, promoting cell survival [29]. Neoadjuvant chemotherapy drugs induce autophagy, which, while not causing cell death, functions as a protective mechanism against drug-induced apoptosis, complicating treatment [30]. Endoplasmic reticulum stress-induced autophagy contributes to drug resistance by clearing misfolded proteins [31]. Autophagy is also induced after DNA damage caused by chemotherapy, reducing cell apoptosis and hindering breast cancer treatment [32,33].
5. Studies targeting autophagy pathways reveal its protective role, and inhibiting autophagy can overcome chemotherapeutic resistance [34]. Autophagy inhibitors, such as 3-MA, Bafilomycin

A1, and chloroquine, used in combination with neoadjuvant chemotherapy drugs, effectively alleviate drug resistance in breast cancer cells [35].

6. Alteration in the drug target in the drug target- Targeted therapies in cancer treatment focus on specific proteins involved in tumor development, making them more precise and less harmful to normal cells compared to traditional chemotherapies. Targeted therapies may lead to resistance through alterations in drug targets due to mutations or changes in expression levels from epigenetic shifts (36). Tamoxifen resistance in ER+ breast cancer can be influenced by decreased ER expression caused by mutations and epigenetic changes (37).
7. Tumor Microenvironment- The tumor microenvironment (TME) is a complex system comprising tumor cells, extracellular matrix, stromal cells, immune cells, and cytokines (38,39). Breast cancer cells within the TME experience hypoxia due to rapid growth and high metabolism, leading to drug resistance (40). The hypoxic TME influences neoadjuvant chemotherapy resistance through cancer stem cells (CSCs) and hypoxia-inducible factor (HIF) (41). HIF-1 α overexpression in TME enhances drug-resistant protein expression, contributing to resistance. HIF-2 α promotes stem cell characteristics, activating WNT and Notch pathways for drug resistance. Hypoxia induces autophagy, further promoting resistance. (42,43,44)

The acidic TME, a result of long-term hypoxia, poses challenges for neoadjuvant chemotherapy. Weakly basic drugs face increased dissociation in the acidic environment, hindering cell entry and causing natural drug resistance. (45) The acidic environment upregulates P-glycoprotein expression, enhancing drug efflux, promoting resistance. (46)

CHALLENGES OF MULTI-DRUG RESISTANCE IN SSA IN THE TREATMENT OF MULTIDRUG RESISTANT BREAST CANCER.

1. Lack of Data and Research: The absence of comprehensive and reliable statistics on both breast cancer and multidrug-resistant breast cancer in SSA due to their poor reportage hampers evidence-based decision-making for healthcare providers and policymakers and makes it challenging to develop tailored treatment strategies.
2. Late Presentation and Diagnosis: Due to factors like limited healthcare access, lack of awareness, and cultural beliefs, patients in SSA often present with advanced-stage breast cancer, which can limit treatment options and decrease overall survival rates.
3. Poor genomic study of cancer in SSA: Limited molecular study of cancer in Sub-Saharan Africa hinders the understanding of drug resistance mechanisms. This scarcity of resources and expertise prevents the identification of specific genetic alterations driving resistance in breast cancer. Addressing this challenge requires investment in research infrastructure and collaborative networks to develop targeted therapies for multidrug-resistant breast cancer in the region.
4. Limited Access to Specialized Care: Many regions in SSA face a shortage of oncology specialists, leading to inadequate access to specialized care for patients with multidrug-resistant breast cancer. This can result in delayed diagnosis and suboptimal treatment.
5. Lack of Advanced Treatment Options: Availability of advanced treatment modalities, such as targeted therapies and immunotherapies, is often limited in SSA. This can hinder the ability to effectively manage multidrug-resistant breast cancer, as these therapies can be critical in cases where traditional chemotherapy is no longer effective.
6. Financial Constraints: The cost of cancer treatment, including drugs, clinical investigations, and supportive care, can be expensive. Many patients in SSA may face financial difficulties in accessing and sustaining their treatment.

7. Inadequate Infrastructure: Health facilities in SSA may lack the necessary equipment, technology, and infrastructure to provide comprehensive cancer care. This includes diagnostic tools, radiation therapy machines, and facilities for surgical interventions.
8. Psychosocial Support: Emotional and psychological support for cancer patients and their families is often lacking in many healthcare settings in SSA, which can be crucial for coping with the challenges of multidrug-resistant breast cancer and encouraging patient to adhere to follow up for treatment, it has been proven that creation of surgical support groups generally improve disease outcome.
9. Stigma and Cultural Beliefs: Stigma surrounding cancer, combined with cultural beliefs about the disease, can influence healthcare-seeking behavior and adherence to treatment regimens, thus affecting the overall outcome of the treatment.

These challenges collectively underline the urgent need for targeted interventions and systemic improvements in breast cancer management in Sub-Saharan Africa.

CURRENT TREATMENT STRATEGIES

Use of P-glycoprotein inhibitor

P-glycoprotein inhibitor Is a member of the adenosine triphosphate-dependent family of transporter proteins ATP-binding cassettes (ABC transporters). The protein is found in a lot of the cells in body (47,48,49), P-glycoprotein (Pgp) channels has been widely implicated as a major player in the development of breast cancer multi drug resistance (50), the protein acts as an efflux channel that actively pump out the chemotherapeutic drugs out of the Target tumor cell (51).

It is known that many tumor types overexpress Pgp (52), which prevents cancer drugs from reaching optimal therapeutics levels in the target cell. Conventional cytotoxic drugs that act in the DNA replication pathways, are particularly prone to the effect of the p-glycoprotein channel (53).

In recent years, researchers have developed P-glycoprotein modulators to counteract the unwanted effects of P-glycoprotein (P-gp) on the removal of chemotherapeutic drugs from cells (54). One notable example is R-verapamil, a medication commonly used in the management of hypertension. However, it's important to note that R-verapamil has been associated with numerous cardiotoxic effects, limiting its applicability (55).

A newer and more promising drug, Tariquidar, has demonstrated its effectiveness in inhibiting P-glycoprotein channels within tumor cells (56). This significant development was elucidated by a study conducted by Ping Zhong et al. Using Folic Acid-Modified Nano-erythrocyte, Ping Zhong's research simultaneously delivered paclitaxel and Tariquidar, showcasing the duo's proficiency in inhibiting P-glycoprotein and thereby enhancing the efficacy of chemotherapeutic agents (57).

This breakthrough holds great promise in improving the efficacy of breast cancer treatments, ultimately offering a more targeted and effective approach to battling multidrug-resistant breast cancer.

Combined chemotherapy.

Combination of multiple chemotherapy drugs with distinct mechanisms of action is has proven to be effective in the management of multi-drug resistant breast cancer (58). It presents a multi-pronged approach wherein each of the drugs has a specific point of attack. An international study investigating the efficacy of lapatinib in combination with capecitabine in the treatment of HER2-positive breast cancer that has advanced despite treatment with trastuzumab and other chemotherapy agents, including taxanes or anthracyclines illustrates this (59).

This approach also allows for the use of lower doses of individual drugs, this reducing the risk of dose related toxicity associated with the use of chemotherapeutic drugs (60).

Also, the combination of drugs has been shown to be synergetic leading to enhanced cancer cell kill rate. The study conducted by Kathy S Albain et al. on Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment demonstrated the superiority of the combined therapy (61). Combination also offers versatility, as oncologists can tailor combinations based on individual patient profiles and the specific resistance mechanisms at play in their cancer cells (58).

Immunotherapy

Cancer immunotherapy has evolved over time to be a vital tool in the management of multidrug-resistant breast cancer with the improved understanding of the immune microenvironment and immunosurveillance (62,63). The targeted cancer cells responses that facilitate tumor death are predominantly mediated via cellular immunity in which CD8+ cytotoxic T lymphocytes (CTLs) are considered the cornerstone cellular element in anticancer immunity. (64) Activated CTLs exert antitumor effects by secreting interferon gamma (IFN- γ) and tumor necrosis factor alpha (TNF- α) along with other cytotoxins (65).

It is worthy to note that tumor cells through immune editing can circumvent this innate tumor inhibitory system (66) by multiple mechanisms including the downregulation of components of antigen processing and presentation machinery leading to loss of major histocompatibility complex (MHC) class I protein expression, low human leukocyte antigen (HLA) class I expression, and defects in T cell receptor (TCR) signaling (67, 68)

Immunotherapies include immune checkpoint inhibitors, T-cell transfer therapy, monoclonal antibodies, treatment vaccines, and immune system modulators (69).

Programmed cell death receptor 1 (PD-1) and programmed cell death ligand 1 (PD-L1) under the immune checkpoint inhibitors class are among the most promising targets for encouraging the immune-system to eliminate cancer cells (70, 71). Examples of this class include Durvalumab, Pembrolizumab, Atezolizumab.

Immunotherapy can be combined with other treatment modalities, such as chemotherapy and targeted therapies. This combination approach has shown promise in further enhancing the effectiveness of cancer treatment, (72) and example is in Peter Schmid et al clinical trial where be concluded that Atezolizumab plus nab-paclitaxel was effective in improving the overall survival of cancer patient with unresectable locally advanced tumor (8).

RECOMMENDATION.

1. Strengthen Primary Healthcare Services: Enhance and optimize primary healthcare infrastructure to serve as cancer registries, ensuring early detection and timely intervention for breast cancer cases.
2. Creating Oncology Specialized Facilities: Increase the number of specialized oncology centers in strategic locations across Sub-Saharan Africa to improve accessibility for patients. Equip these facilities with state-of-the-art technology and skilled healthcare professionals.
3. Public Health Promotion: Implement comprehensive public health campaigns to raise awareness about breast cancer, its risk factors, and the importance of early detection. Encouraging regular breast cancer screenings through educational programs and community outreach.
4. Invest in Cancer Research: Allocate substantial funding for cancer research, with a focus on understanding the genomic basis of breast cancer in the local population. Fostering collaborations between research institutions, healthcare providers, and policymakers to accelerate progress in breast cancer treatment.

6. Patient Support Networks: Establish robust support networks for breast cancer patients, including survivorship programs, counseling services, and peer-to-peer support groups, providing resources for patients and their families to navigate the physical, emotional, and financial challenges associated with cancer treatment.
7. Access to Affordable Treatment: Advocate for policies that improve access to affordable cancer treatments, including chemotherapy drugs, targeted therapies, and immunotherapies. Exploring partnerships with pharmaceutical companies and international organizations to negotiate fair pricing for essential cancer medications.
8. Comprehensive Palliative Care: Integrate palliative care services into cancer treatment plans to alleviate pain, manage symptoms, and improve the quality of life for patients with advanced breast cancer also ensuring training of healthcare professionals in palliative care practices to ensure comprehensive support for patients and their families.
9. Cultural Sensitivity and Education: Promote cultural competence among healthcare providers to better understand and address cultural beliefs and practices related to cancer, offering educational resources in local languages helps to increase health literacy and empower patients to make informed decisions about their care.
10. Long-term Monitoring and Data Collection: Implement systems for long-term monitoring of breast cancer patients to track treatment outcomes, monitor for recurrence, and assess long-term survivorship. Regularly update and maintenance of a comprehensive databases on breast cancer incidence, treatment outcomes, and multidrug resistance patterns for evidence-based decision-making.

By implementing these recommendations, Sub-Saharan Africa can take significant strides towards improving the management of multidrug-resistant breast cancer and enhancing the overall well-being of affected individuals and their communities.

CONCLUSION

Breast cancer management in Sub-Saharan Africa unveils a complex landscape marked by challenges and potential solutions. Multidrug resistance (MDR) poses a formidable threat, jeopardizing the positive impact of existing treatments. Despite commendable strides in breast cancer care, the region faces unique challenges, necessitating nuanced interventions. Our exploration underscores the urgent need for improved data collection, early diagnosis, enhanced genomic studies, and greater access to specialized care. Financial constraints and cultural factors add complexity, urging a holistic and culturally sensitive approach. On the pharmacological front, promising advancements in P-glycoprotein inhibition, combined chemotherapy, and immunotherapy offer hope. Tariquidar's potential against MDR and the synergy of combined chemotherapy showcase evolving strategies. Immunotherapy emerges as a beacon for future advancements. Our recommendations form a roadmap for progress, emphasizing primary healthcare strengthening, specialized oncology facilities, and research investment. Public health campaigns, affordable treatment access, and comprehensive palliative care address multifaceted challenges.

As we conclude, a resounding call to action echoes. Overcoming multidrug-resistant breast cancer demands collaboration from healthcare professionals, policymakers, researchers, and communities. Embracing these recommendations can transform the breast cancer narrative, offering renewed hope to countless lives in Sub-Saharan Africa.

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