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HEAD AND NECK CANCER CHEMOTHERAPY IN NIGERIA

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Introduction

Chemotherapy is defined as the use of one or more chemical compounds in treatment of neoplastic diseases to destroy offending cancer cells without damaging the host. Chemotherapeutic agents (also known as cytotoxic drugs) can be used to cure cancer, lessen the chance of cancer recurrence, stop or slow down its growth.

The place of chemotherapy in head and neck cancer continues to evolve and broaden over the last two decades. Since the advent of platinum-based chemotherapeutic agents in the late 20th century, the role of chemotherapy has gradually evolved from producing short-lived local responses in the palliative setting to the widely used curative multimodality regimes for advanced head and neck cancers. Other forms of cancer treatment that is being used along with chemotherapy include surgery, radiotherapy, hormonal therapy, immunotherapy etc.

Targeted cancer therapy, like conventional chemotherapy, use pharmacological agents that inhibit growth, increase cell death and restrict the spread of cancer. Targeted therapies interfere with specific proteins involved in tumorigenesis thus focusing on specific molecular changes which are unique to a particular cancer. This form of therapy holds great promise to improve patient outcome while limiting toxicity and treatment exposure. The best known targeted therapies for head and neck cancers include: Epidermal growth factor receptor (EGFR) monoclonal antibodies (cetuximab, panitumumab, zalutumumab and nimotuzumab), EGFR tyrosine kinase inhibitors (gefitinib, erlotinib, lapatinib, afatinib and dacomitinib), vascular endothelial growth factor (VEGF) inhibitor (bevacizumab) or vascular endothelial growth factor receptor (VEGFR) inhibitors (sorafenib, sunitinib and vandetanib) and

inhibitors of phosphatidylinositol 3-kinase/serine/threonine-specific protein kinase/mammalian target of rapamycin^{4, 5, 6}. Currently, only EGFR inhibitors have been approved, the others are under investigation in clinical trials. These drugs have been reported to have limited efficacy in some patients. Nevertheless, inhibition of EGFR has been shown to improve overall survival, and EGFR inhibitors are routinely administered in this tumor type.⁶

Mechanism of action of chemotherapy in head and neck cancers

A cell divides by progressing through a sequence of steps called cell cycle and its various phases. Almost all chemotherapeutic agents act on one or more phases of the cell cycle by disrupting some aspects of cell growth cycle. Chemotherapeutic agents can therefore be classified as phase specific and phase nonspecific. In addition, chemotherapeutic agents typically act by interfering with basic cellular processes that are usually associated with mitosis. Therefore, they selectively act on rapidly dividing cells and affect tissues with high turnover.⁷ There is thus a degree of synergy with radiotherapy and scope for combinations of agents with differing mechanisms to work synergistically.

Chemotherapy is indicated if a patient has a chemotherapy responsive disease that may shorten his/her survival. Most of the head and neck cancers are squamous cell cancers and the drugs found effective are methotrexate, carboplatin, cisplatin, bleomycin, docetaxel, hydroxyurea and 5-fluorouracil. Adriamycin has been used for certain non-squamous carcinomas (e.g. adenoid cystic carcinoma) and dacarbazine for melanomas. Lymphomas of the head and neck (both Hodgkin and non-Hodgkin types) are also treated by chemotherapy



because of their multifocal origin and widespread involvement.⁷

Management of head and neck cancers

The gold standard for head and neck cancer treatment is multimodal with the use of surgery, radiotherapy, chemotherapy and often involves the maxillofacial surgeons, otolaryngologists, histopathologist, dentists, nurses, psychiatrists, therapists, social workers, and others.⁸ Chemotherapy drugs are either given as single therapy or in combination with other therapies. Different modalities of treatment include induction chemotherapy, concomitant/concurrent chemotherapy and neoadjuvant chemotherapy.⁹ Studies have shown that concurrent chemoradiation offers the best chance of survival and local cure of head and neck cancers especially the squamous cell carcinoma.^{9,10}

The histologic cell type and the stage of the disease determine the choice of treatment. Lymphomas respond well to chemotherapy. Treatment of early stages (Stage I and II) of head and neck carcinomas can be aimed at cure with radiotherapy alone or surgery alone. However, stages III and IV carcinomas require a combination of salvage surgery and chemoradiation.⁹ Chemotherapy is also useful in cases of metastasis and recurrence. New standards for management of locally advanced disease employ platinum-based chemotherapeutic agents such as cisplatin and carboplatin with radiotherapy. The intent is to preserve head and neck functions such as speech and swallowing.¹¹ In his work on head and neck cancer pathology, Alfouzan¹² found that HPV-related head and neck cancers are more responsive to chemotherapy than HPV-unrelated cancers. They are also more susceptible to immune surveillance of tumor-specific antigens.

Modalities of chemotherapy in Nigeria with its challenges

In Nigeria, the following are the commonly used chemotherapeutic drugs: Cisplatin, Paclitaxel, Capecitabine, Adriamycin (doxorubicin hydrochloride), Bleomycin, Carboplatin, 5-fluorouracil, Cyclophosphamide, Cytarabine, Etoposide, Flutamide etc. In most centers in low and middle income countries, surgery is still the mainstay of treatment of head and neck cancers as few places possessed the facilities for chemotherapy and radiotherapy.¹³ Ironically, reconstructive surgery is also financially out of reach for most patients even when suitable technical expertise is available, as more

than 60% of Nigerian pay out of pocket for their health care compared to 16.8% in the United Kingdom. Studies have shown that in spite of several decades of progress and improvements in treatment and supportive care, the prognosis has remained unacceptably low for this group of patients stagnating at about 50% 5 years survival rate.^{8,13}

According to the National Cancer Control Plan in Nigeria,¹⁴ the absence of a well-structured tumor board at the comprehensive cancer care centers affects the quality of care cancer patients receive. Nigeria only has eight public and one private comprehensive cancer care centers. These comprehensive cancer care centers are expected to offer pathology, molecular and imaging diagnostics, with any or a combination of surgery, chemotherapy, radiotherapy and nuclear medicine services as part of treatment for cancer patients. Most times, these centers are non-functional because the machines are down which further worsens the timely access to treatment in Nigeria. The country does not have medical oncology as a specialty rather those trained as radiation oncologist also have training in the administration of chemotherapy. In some centers, the surgeons administer chemotherapy to their patients.¹⁴

A study by Nwagbo *et al.* revealed that knowledge of chemotherapy was insufficient among health workers in Nigeria. Nurses who can provide care to patients receiving chemotherapy require specialized knowledge to ensure safety of patients and themselves as well as the environment.¹⁵

Furthermore, treatment is usually palliative in Nigeria since majority of patients present late. Considering different scenarios related to each patient, stage at presentation, extent of the disease, organ involvement, histological type, co-morbidities, performance status, etc., patient's therapies are better individualized. On the study of the pattern of comorbidities in cancer patients, Salako *et al.* found that the comorbidities are also associated with a significant drop in functional reserves and an increased physical frailty, which suggest the reasons why cancer patients in developing countries like Nigeria experience higher levels of treatment-related toxicities and suboptimal outcomes.

In Nigeria, cancer is often being perceived as end to one's life simply because of series of reasons including poorly equipped hospitals, lack of knowledge on the part of the people, lack of trained oncology human resource, lack of chemotherapeutic drugs and high

cost of treatment, limited screening centers, government's poor attitude towards policy formulation and implementation.

Adverse effects and treatment failures associated with chemotherapy administration

Cytotoxic drugs not only kills fast growing cancer cells, they also act on rapidly dividing healthy cells as those of hair follicles, gastrointestinal mucosa and bone marrow leading to some adverse effects in the body system.⁷ Acute adverse effects like vomiting, diarrhea, malaise, nausea, anorexia, fever, anaphylactic reaction, cytopenia, tumour lysis features and late adverse effects like bone marrow depression, alopecia, amenorrhea, infertility, second malignancy are associated with chemotherapy. Some drugs have selective action on kidney (methotrexate, cisplatin), nerves (vincristine and cisplatin), heart (adriamycin) and bladder (cyclophosphamide).⁷

Researchers have confirmed that side effects associated with cancer chemotherapeutic agents can occur depending on the chemical and physical properties of the drugs, the quantity administered, and the available collective and personal protective measures. Other factors such as the health practitioners' skills and knowledge also significantly determine the level of risk. It follows that recurrent exposure to even low doses for long period of time may produce profound effects.¹⁵ In cases of advanced head and neck squamous cell carcinoma where locoregional control has been achieved with chemotherapy, the long-term prognosis is still disappointing, with second primaries and metastatic disease accounting for a large proportion of treatment failures.

The poor tolerance of chemotherapy in the elderly cancer patients is associated with declining organ function with resultant changes in the pharmacokinetics and pharmacodynamics of cytotoxic drugs and increased susceptibility of certain organ systems to therapeutic complications. The National Cancer Center Network (NCCN) guidelines for the treatment of elderly patients with chemotherapy advise dose adjustment according to individual glomerular filtration rate (GFR), prophylactic use of granulocyte colony stimulating factors and maintenance of hemoglobin level of ≥ 12 g/dL. These are not readily feasible in most of the patients in our environment and may account for the high morbidity and mortality in patients receiving chemotherapy. Adewuyi *et al.* recommended the use of

chemotherapy, which is less toxic but more effective, for the elderly patients and need for adequate supportive treatment using infusions, analgesics, blood transfusion as the need arises within the available resources.¹⁹

Pharmaceutical care of head and neck cancer patients

The provision of medicine and therapeutic information service by clinical pharmacists in oncology care setting is essential for unbiased and patient-specific medicine information which helps in improving patient care.²¹ Clinical pharmacists can provide medication related advice and in collaboration with physicians, develop personalized treatment plans.

The most common side effects of chemotherapy include nausea, vomiting, fatigue and myelosuppression, with approximately 50% of these side effects being preventable.²² Participation of Clinical pharmacists in a multidisciplinary oncology team may improve the overall care of, and enhance medication adherence in head and neck cancer patients.²³⁻²⁵

Recommendations

A study in South West Nigeria has recommended the need for continuous and periodic update of knowledge about chemotherapy and its administration guidelines to alleviate its adverse effects among cancer patients.¹⁸ There is therefore a need for future research to explore more medical oncology training of respondents as well as involve more centers, to provide evidence to support policy enactment. Chemotherapy drugs are expensive in Nigeria. The National Health Insurance Scheme (NHIS) plans to increase their coverage to include chemotherapeutic drugs should be implemented as soon as possible. The promising, novel treatment option for patients with squamous cell head and neck cancer is molecular-targeted therapies⁶ thus the inclusion of targeted therapy in the management of head and neck cancers patients in Nigeria should be considered. The involvement of clinical pharmacists in management of cancer patients should be encouraged; the provision of adequate and appropriate pharmaceutical care will ensure a better therapeutic outcome in cancer patients. The implementation of medicine and therapeutic information (MTI) service as an integral part of oncology pharmacy services is highly essential. The Government should provide dedicated funds for equipping selected centers in the country to provide comprehensive cancer treatment.

This will significantly reduce the burden of the cost of cancer treatment and encourage head and neck cancer patients to adhere to chemotherapy treatment. Current research on head and neck cancer is geared towards the identification of molecular markers, which are connected with the response to the treatment used. This will aid personalized targeted and non-targeted treatment; Nigerian pharmacologists and pathologists should seek research grants to carry out studies in this area.

Conclusion

Generally, cancer remains a very traumatic diagnosis and its treatment is very expensive. The Government should endeavour to alleviate the suffering of cancer patients by providing improved treatment opportunities at subsidized rates. The palliative care component of head and neck cancer control with chemotherapy needs further emphasis in Nigeria because many of our cancer patients have no hope of cure as they present to hospital late, which makes the disease far advanced at presentation. When cure is no longer feasible or curative treatments cannot be made available or affordable. Palliative care then remains the only source of succor.

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