Management of Cervical Cancer in Sub-Saharan Africa

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Cervical cancer (CC) is the most common viral infection of the reproductive tract and in Sub-Saharan Africa (SSA), its morbidity and mortality rates are high. High HPV vaccine coverage can be achieved using the class school-based strategy with opt-out consent form process. Barriers to CC screening uptake included lack of knowledge and awareness and unavailability of screening services. The reasons for late-stage presentation at diagnosis were unavailability of screening services, delaying whilst using complementary and alternative medicines and poor referral systems. The challenges in chemotherapy included unavailability and affordability, low survival rates, treatment interruption due to stock-outs as well as late presentation. Major challenges on radiotherapy were unavailability of radiotherapy, treatment interruption due to financial constraints, and machine breakdown and low quality of life.

cervical cancer management screening diagnosis chemotherapy radiotherapy human papillomavirus vaccine

1. Introduction

Cancer of the cervix is the most common cancer affecting women in Sub-Saharan Africa (SSA) [1]. Cervical cancer (CC) is caused by persistent infection with Human papillomavirus (HPV), whose genome proteins E6 and E7 inactivate tumor suppression genes pRb and p53 leading to cervical intraepithelial neoplasia (CIN) which will then develop into invasive CC [2]. It takes approximately 10 to 20 years from CIN to invasive CC [3]. Every year, about 500,000 women are diagnosed with CC worldwide and approximately 311,000 die from the disease [4]; 85% of the deaths occur in low-income countries (LICs) [5]. Incidence of CC is high with an average of 20.1% in SSA compared with 15.8% world-wide; CC related deaths at 13.8% for SSA and 8.2% worldwide [6]. Cervical cancer is insidious in its onset and slow in its progression but poses serious health outcomes like maternal and child mortality and morbidity. The pathway from symptom and signs recognition, care seeking, diagnosis and treatment is a process composed of events and processes that are influenced by different factors like demographics, health care system and disease factors.

Human papillomavirus infection is the most prevalent viral disease of the female reproductive tract [7]. Traditionally, CC prevention was composed of screening and early diagnosis but now, in high-income countries (HICs), HPV vaccine has become an integral part of CC prevention. The discovery of the HPV vaccine availed an opportunity to decrease morbidity and mortality associated with CC. Almost 99% of CC cases are caused by HPV, with HPV 16

and 18 causing seventy percent of the cases [7]. In Africa, there is limited access to screening and treatment [8] hence it is important to vaccinate girls against HPV as protection against CC. In SSA, preadolescent girls are not routinely included in the Expanded Program on Immunization (EPI) hence strategies for the delivery of the vaccine need to be explored. As of June 2018, only eight countries in SSA had a national HPV immunization program [9]. Rwanda reduced a two-decade gap in vaccination between HICs and LICs to five years [10]. In SSA, approximately 18.6 million school-aged girls are not in school [11] hence strategies to reach out to these girls are needed.

Early detection of CC is important because of the relationship between stage at diagnosis and survival rate. Women in developed countries have a two hundred and eight percent greater chance of being treated successfully for CC compared with women in Low- and Middle-Income Countries (LMICs) because of late presentation at diagnosis [12]. A five-year survival rate of 91% can be achieved if the patient is diagnosed with localized CC and the survival rate falls to 57% for regional and distant disease stages [13] hence the need to find out why women present with late-stage CC at diagnosis. Women who have HIV infection develop CC 10 years earlier than HIV-negative women; incidence of CC is about 900 per 100,000 in women with AIDS compared with 10 per 100,000 in the general population [14], hence the need to screen them yearly. Highly effective anti-retroviral therapy prolongs survival among those who are HIV-positive but does not prevent them from developing CC [15]. It is always important to keep checking how HIV positive women are coping with chemotherapy and radiotherapy, and to find any new evidence pertaining to CC treatment of such women.

In SSA, there is lack of timely cancer registries and incomplete risk factors for profiling [4]. Poor quality data curtail reliable population-based estimates for mortality rates, incidence rates and effectiveness of interventions. Of the twenty LMICs globally with the highest incidence of CC, sixteen are African countries [16]. The overall estimated standardized incidence rate is 35 per 100,000 women, and 23 per 100,000 women die from CC [17]. CC is a disease of the poor, showing evidence of inequities of access to health care [18]. CC mortality can be reduced by screening but ensuring high coverage of screening services is a serious challenge in LMICs, so there is a need to find out barriers to screening uptake. Coverage of CC screening is lowest in LMICs, estimated to be 19% [17]. Screening all women in a target age group every three years can prevent 91% of CC cases [19]. Screening is very crucial because CC takes 10–20 years for pre-cancer dysplasia to develop into invasive cervical cancer [14]. It is important to try and break barriers to screening after identifying the barriers.

CC patients in SSA present at an advanced stage which automatically precludes surgery as a treatment option in most patients [20]. Concomitant chemotherapy and radiotherapy with cisplatin as the radio-sensitizing drug is the standard of treatment for CC [21]. The efficacy of drugs for chemotherapy depends on delivering a full dose of treatment cycles for the required number of times continuously [22]. In SSA, women mostly present with advanced CC which needs standard curative treatment, which includes external beam radiotherapy, brachytherapy and with or without chemotherapy [14]. It is very crucial to keep checking the status of chemotherapy and radiotherapy services so as to maximize treatment outcomes based on available current treatment evidence.

Like chemotherapy, success of treatment using radiotherapy needs the completion of the cycles of the appropriate dose religiously. There is a potential for converting some patients from palliative to curative with radiotherapy and

brachytherapy treatments, and the challenges facing such treatment options in SSA are worth solving [23]. Radiotherapy, like any other form of treatment, should improve the quality of life of CC patients [24]. Survival rate is another good measure of effectiveness of treatment [25]. Death rate per 100,000 women in SSA is twelve times higher than it is in Western Europe (25.3% vs. 2%) [26]. CC is a symbol of global health disparity [25] but can be reduced by finding the best method of treatment and prevention as well as finding out what causes these women to seek help late.

2. Management of Cervical Cancer in Sub-Saharan Africa

The HPV vaccine is an acceptable form of CC prevention and high coverage can be achieved using the school-based strategy, with out-of-school girls being reached using local health centers [27][28][29][30]. Reasons for late presentation included unavailability of screening, delaying seeking health care whilst going to traditional healers and faith healers, fear of CC diagnosis, health professional misdiagnosis, lack of knowledge about CC and negative cultural beliefs [12][31][32]. Barriers to screening uptake were lack of knowledge about CC, unavailability of screening services, fear of positive results, misconception about screening procedures and negative cultural beliefs [33][34]. The status of chemotherapy was bad, characterized by unavailability, affordability and accessibility challenges [22]. The situation was worsened by most patients presenting with late-stage disease, side effects and lack of investigating services due to financial reasons [15][20]. The major outcomes were poor survival rates and high mortality rates [21]. Radiotherapy status was bad, with the major aspect being the unavailability of radiotherapy services due to high demand, machine breakdown and the outdated aspects of the machines exposing patients to a lot of side effects [25][26][35].

The school-based strategy works well in countries like South Africa where primary school level is compulsory and universal [36]. The grade to be chosen should be based on the fact that the girls to be vaccinated are not yet sexually active and have reached an appropriate age to understand sexual education. Community involvement such as including chiefs and religious leaders and social mobilization, micro planning, health promotion and health informatics were major contributors to high coverage [9]. For the good of the girls, consent process might need to be waived, especially where religion and culture are the limiting factors. Opt-out vaccine consent process produced higher coverage compared to opt-in models [36]. Teachers can be empowered to be vaccine champions in disseminating information about HPV vaccine as well as CC in their community. HPV vaccination program needs a well-established vaccine delivery mechanism with adequate transportation, cold chain, human resources and capacity to monitor the whole process.

More still needs to be done in SSA as far as the HPV vaccine rollout; by December 2017, only 3 countries, South Africa, Uganda and Rwanda, had transitioned from the pilot to national program [11]. Vaccine hesitance was mainly due to the fact that the vaccine was relatively new, that it will cause the girls to be promiscuous and that it was considered inappropriate to target young girls to prevent sexually transmittable diseases [37]. A positive attitude towards the HPV vaccine was a strength which contributed to high coverage. Mother–daughter approach is not an efficient way to deliver vaccine since maternal CC screening is more time consuming than HPV vaccine and in one of the studies, 3000 women were screened versus 2000 girls that were vaccinated [8]. Vaccination was seen as a

culturally acceptable form of CC prevention as some women found the practice of CC screening embarrassing, too intimate and uncomfortable [38].

Absence of a nationally organized screening program (opportunistic screening) and lack of money for CC treatment caused women to not seek health care early until symptoms become worse. The average prevalence of late-stage presentation was 71%. The Model of Pathways to Treatment (MPT) explains well how the delays occurred through: appraisal, help-seeking, diagnostic and pre-treatment [39]. Public awareness campaigns for the women and continuous professional development (CPD) for the health care professionals can be used to deal with these delay intervals.

The core strategies to prevent late-stage presentation by CC patients include population-based CC screening and prompt treatment of pre-invasive cervical lesions [39]. Poorly differentiated histology is an intrinsic tumor characteristic which cannot be easily modified hence the need to intensify screening and reduce both patient and institutional delay. Spending time trying to treat cancer using traditional medicines was cited as a factor contributing to late presentation by CC patients [40] hence the need to train traditional healers with basic training to alert them to CC symptoms so that they can quickly refer women with CC to health care centers. Community leaders must also be educated about CC for them to be able to give accurate information to assist in identification of CC which is often overlooked.

Health professionals were also a contributing factor to late-stage presentation as some health personnel were not aware of CC. It took 6 to 12 months for referrals to take place [41]. Women cannot solely be responsible for late presentation because lack of suspicion of CC by health care professionals and the lack of prioritization of CC management by health departments were major contributors to presentation of advanced stage at diagnosis [42]. Women's health issues that are not related to maternity or family planning lacked priority. Information regarding the link between CC and sexual activity is important to allow women to make an informed decision about their sexual behavior.

Due to molecular interactions between HIV and HPV, CC is an HIV/AIDS defining disease [43][44], hence the need to integrate routine HIV care with CC screening as HIV- positive women are recommended to be screened for CC yearly [45]. Routine reminders and appointments for screening for HIV-positive CC patients are needed instead of relying on the patients' initiatives. Cell phones can be used for such reminders. Standard doses for chemo radiotherapy can be considered as the standard of care for appropriately selected HIV-positive women with CC [21]. The role of CC survivors in advocacy and mobilization for CC treatment and screening cannot be overemphasized since knowing someone with CC was associated with knowledge about CC and high levels of screening [27]. Lack of knowledge about CC was a major barrier to CC screening, hence the need to increase health education about CC which is hoped to translate to an increase in screening uptake but knowledge does not always translate to practice as in some studies where many of the health professions were never screened themselves [32].

Awareness campaigns and education must be undertaken by health professionals since motivators for screening included the doctor's recommendation, fear of death from cancer and affordability [33]. A new curriculum for health

care professionals is needed which includes prevention and intervention for both non-communicable and communicable diseases. CC screening discussion should be mandatory between health workers and women whenever they seek any health care. The health education has to be user-friendly, as 8 million people in SSA were not able to benefit from existing written health promotion material due to illiteracy [46]. Educational campaigns must focus on increasing risk perceptions, improving attitudes and educating women to seek screening when they are free from signs and symptoms of CC, as it was found out that success of the screening program depends largely on CC knowledge and health-seeking behaviors [47].

Cost of screening was cited as a barrier to screening uptake so there is a need to subsidize screening costs or make it completely free since some studies included transport costs as a screening barrier [48]. Religious and cultural factors were a barrier to CC screening uptake as they affected health-seeking behaviors and practices like early marriages, and onset of sexual activities present the need to protect the girls by using the HPV vaccine. Socio-cultural beliefs resulted in women's perception of low threat of CC. An individual's perceptions on health issues can also hinder health behavior like CC screening [49], hence the need to educate women. CC awareness needs to consider varying religious and cultural beliefs in order to implement an effective CC screening program.

The unavailability of screening services was a major barrier so there is a need to offer screening services from Monday to Friday so that clients are not turned away because the services are offered on certain days. Governments in SSA need to honor their commitment to the Abuja declaration which provides for 15% of their national budget to health [50]. Lack of epidemiological data, cancer service policies, human resources, financial resources and political will were barriers which can only be addressed by the government. The incidence rates ranged from 22/100,000 to 76/100,000 women, and mortality rate ranged from 18/100,000 to 50/100,000; such figures can only be reduced with strong political will and mobilization of resources to build capacity for screening and treatment [51].

Chemo radiotherapy using cisplatin as the radio-sensitizing agent was the standard of care for CC treatment and all effort should be made to avoid tenofovir because of overlapping, neurological, renal toxicities and hematologic with cisplatin [21]. The human life loss due to stock-outs of chemotherapy drugs that are used to treat CC is quite significant since efficacy of these regimens depends on taking a full dose per schedule for a required frequency of treatment cycles; this includes administering fewer cycles, delays in cycles or absence of any of the drugs which will reduce the curative potential to zero [22]. Interruption of treatment can cause the patient to go out of remission and in some cases, remission will not be achieved on reinstitution of the drug and the ultimate result is an unnecessary loss of life. A low proportion of CC patients benefit from chemotherapy due to late presentation in developing countries, hence the need for a national screening program as opposed to opportunistic screening [15]. This late presentation at diagnosis also precludes the use of surgery as a treatment option for CC [20].

In Africa, Ethiopia has the second largest gap, after Nigeria, between the availability of and demand for radiotherapy machines; judging from the WHO recommendations, there are 73 radiotherapy units missing in Ethiopia which had just one machine for the whole country [26].

Breakdown of radiotherapy machines was a major problem in CC treatment since this causes treatment interruptions [51]. There is a need for a clear policy to deal with treatment interruptions. Cost of chemo radiotherapy was the most difficult challenge faced by CC patients which can be sold by the governments in SSA, subsidizing CC treatment since most patients cannot afford it. Despite increased toxicity, chemotherapy and radiotherapy are widely accepted as a major treatment for CC [49].

Deterioration of quality of life occurs because of the diagnosis of late-stage CC and due to treatment, hence the need for management services that ensure coping with CC for both patients and home-based caregivers [40]. Counseling must be integrated in management of CC patients and relatives to enhance coping at all stages of CC care. Expensiveness of chemotherapy resulted in it not being regularly included in chemo radiotherapy; this lack of therapeutic options and early detection activities resulted in low probabilities of survival like a range of 5-year survival of 2.9% to 22% in SSA compared to 68% in the USA [25]. The exclusion criteria for a patient to undergo chemo radiotherapy included anemia, hydronephrosis and impaired renal function [48]. The other factors that contributed to low survival rate in SSA included factors like the 28 countries which did not have a radiotherapy facility, and where they did have, the radiotherapy machine was not adequate; 30% of radiotherapy machines were Cobalt60 units instead of intensity modulated using linear accelerators which are the standard of care as they reduce side effects due to unnecessary irradiation of the surrounding tissues [26]. Brachytherapy was available in 20 of 52 African countries [26].

The key factors that cut across all themes are as follows:

- limited or absence of necessary infrastructure and financial resources,
- behavioral issues of patients—religion, societal view shaping the behavior,
- lack of knowledge and skills—on the side of patients and health professionals, respectively,
- poor planning and governance on the side of governments in these countries.

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