Is cytotoxic chemotherapy for lymphoma currently feasible for patients in Malawi? A debate

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Abstract

There is currently no systematic provision for chemotherapy of adult patients with cancer in Malawi. Is the introduction of such a service now feasible in Malawi, and should an individual patient with potentially treatable disease be given chemotherapy in the absence of such a service? The technical, economic and moral issues are discussed here in the form of a debate.

Introduction

A 36 year old HIV positive patient who has recently started on antiviral therapy and is currently in good general health presents with several months history of an enlarged cervical lymph node. Lymph node histology is reported as showing a high grade non-Hodgkin's lymphoma (NHL), and staging investigations indicate that disease is localised.

In the developed world, a good prognosis patient such as this would be expected to do well with cytotoxic chemotherapy and continuing antiretroviral therapy, with a reported 5 year survival of 47% with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) chemotherapy[1].

There is no systematic provision for chemotherapy for adult patients in government hospitals in Malawi, but the drugs that constitute CHOP chemotherapy are currently in the pharmacy. Should the patient be given this combination therapy, in the context of our available resources and facilities?

For

Dr Y Mlombe

Yes, when the patient has made an informed decision for treatment

Cancer is becoming an epidemic in the developing world[2,3-5]. Cancer mortality ratios are much higher in Africa than in the West[2]. The majority of African patients present with advanced disease when cure is unlikely[2,5]. To save lives cancer patients in Africa must have improved access to proven, cost-effective therapy, efficiently delivered[2]. The cost effectiveness of CHOP can be demonstrated by the fact that the World Health Organisation (WHO) model list of essential medicines, which is aimed at resource limited settings, includes the drugs[6] which are in the CHOP regimen. To encourage early diagnosis of cancer, it is essential that patients diagnosed with early-stage cancer have immediate access to treatment[2]. A study carried out in Zimbabwe demonstrated that African Zimbabweans had worse cancer survival rates than European Zimbabweans on account of differential access to cancer treatment (and not on account of side effects)[7].

The patient under discussion has presented early with disease which, without adding chemotherapy to his highly active antiretroviral therapy (HAART) treatment, will definitely kill him within months[8], but with the addition of CHOP he stands a 40% chance of being cured – a chance similar to that of an HIV negative NHL patient1,[9-15]. This patient should be offered CHOP, which is available, and be given it if he accepts. After all, some resources have already been utilised to get the CHOP drugs into the hospital; and considerable effort has been taken to obtain a biopsy, to do histology and to perform staging investigations in this patient. Death looks different from a distance[16], and in this situation the expected *personal ethics of care* of a doctor should be upheld by asking the one staring death in the face (the patient) to decide about treatment or no treatment issues. Apart from autonomy, other treasured health care values to be considered in this patient include dignity, prevention of complications of disease, access, justice, cost control and equity in provision of care[17].

Denying a poor and helpless Malawian cancer patient access to available and potentially curative treatment is not a humane thing to do. Chances are that if this patient had power and influence he would travel abroad anyway to countries like South Africa to get CHOP, most likely using public funds. This is very expensive because it must include patient and guardian air-tickets, hotel accommodation, allowances and exorbitant hospital charges for foreign patients. It is also not effective because chemotherapy regimens involve several cycles repeated at regular intervals. Patients may be sent to South Africa initially and then fail to go again weeks later, or they may go again so late that the benefits of their initial cycle(s) are negated. Such practice more often than not proves that *poverty can be expensive*.

Statements like "Chemotherapy won't work in Africa ….because of economics. We have to look at what we can do at the moment, and that is to improve palliative care"[18] are misleading[19]. Chemotherapy has not worked 100% in the West and some patients in the West endure some of the most horrible side effects for the hope of some benefit only to end up dying[20], and yet cytotoxic chemotherapy is still used[21-23]. It is ironic that we should have to justify chemotherapy for the treatment of aggressive lymphoma in Africa when it was Dr Denis Burkitt who pioneered treatment of aggressive lymphomas by experimenting on African children in Uganda[24]. Palliative care has many definitions most of which include relief of symptoms. Relief of symptoms includes the provision of chemotherapy when curative intent has been abandoned or is not realistic in NHL[25]. Some definitions equate palliative care with hospice (terminal) care. Yet other definitions equate palliative care with supportive care which can be given along side curative treatment. Neither of these two kinds of palliative care would be applicable to this patient at this point in time, because his lymphoma is potentially

curable with drugs which are available. Cancer management services are and should be progressive[19]. Pathologists and laboratory personnel can be motivated to improve the diagnostic workup of cancer patients once they know that such patients can be offered treatment.

Malawi has had at least one haematologist since the early 1990s. Just as a cardiologist does not need to be a qualified diagnostic radiologist in order to perform an echocardiogram, a general surgeon does not need to be a qualified oncologist in order to perform mastectomy for breast cancer. Similarly, a (clinical) haematologist does not need to be a qualified oncologist in order to treat a patient with NHL. Training for Masters in Internal Medicine in countries within the African region such as Kenya, where they have hospitals with haematology and oncology wards and clinics under the department of Internal Medicine, involves hands-on experience in administration of chemotherapy to cancer patients. CHOP for lymphoma is generally safe to such an extent that it is mostly given in outpatient settings in hospitals in Kenya. CHOP can be toxic, and febrile neutropenia can occur but does not always occur. Attempts to find completely non-toxic ways of treating aggressive lymphoma within Africa have never succeeded at eliminating possibilities of febrile neutropenia while maintaining acceptable cure rates[26]. It is instructive to note that HAART toxicity (including febrile neutropenia) can kill patients more than AIDS itself, and yet patients in Malawi are still offered HAART[27].

Suboptimal, inferior or unproven cytotoxic chemotherapy may expose patients to side effects without real benefit, may be harmful or may create drug resistance. Giving vincristine alone, for example (instead of CHOP), to the patient in question in the hope that this would provide some kind of "care" is like giving a smear positive tuberculosis patient ethambutol alone or giving an HIV positive patient AZT (which was used as monotherapy for treatment of HIV in the West in the past) in the belief that such treatment will help the patient. As far as cytotoxic chemotherapy is concerned, the same principles which apply in wealthy countries must apply in resource poor settings[17] i.e. only standard, evidence-based or expert panel recommended protocols should be administered to cancer patients or else patients should be entered in clinical trials.

Against

Dr. E Crutchlow

'Just because you can, doesn't mean you should.'

I do not categorically disagree with offering cytotoxic chemotherapy for cancer in Malawi; but any service would need to be safe and sustainable.

In an infrastructure-poor setting, a service offering a combination of strongly immunosuppressant drugs needs to be carefully administered, monitored and audited. Cytotoxic chemotherapy is a potentially dangerous tool even in infrastructure-rich settings and introducing it in a country where even basic hospital care is often not provided adequately, is in my view inhumane. There are new therapies emerging that are more effective and less toxic but these are prohibitively expensive in most developing countries[28].

Giving drugs to patients and not being able to safely monitor them or effectively deal with side effects and complications is not safe. Chemotherapy requires hospital infrastructures and technical expertise, yet most African countries lack the ideal framework to administer these treatments[5]. The key concepts of ethics in medicine are autonomy, justice, beneficience and non-malefience ('do no harm') and giving CHOP in our setting, is in my view not meeting the standard of due care.

There is no doubt that if the resources were available then the option of chemotherapy should be open to all Malawians who need it. But the resources *are not* readily available; difficulties with diagnosis (long waits for lymph node biopsy); unreliable availability of drugs (cyclophosphamide currently out of date and limited stock, allopurinol also out of stock); unreliable blood test results; limited blood transfusion services; no qualified oncologist; no specialist nurses and no space for a designated isolation room for neutropenic patients. CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, prednisolone) has been shown to cause febrile neutropenia in 21% of those under 65 years[29] and this is in a nutritionally robust and mostly HIV naïve American population.

Systems still need to be instigated and improved to achieve routine high quality care of our patients on the wards, and until the relatively simple can be mastered there is little point and a degree of risk in adding to the already overstretched resources.

Although in itself the HIV/AIDS pandemic should not affect the provision of cytotoxic chemotherapy to Malawians, it certainly may make their management more difficult. Our population here is undoubtedly different from that seen in the West, and administering cytotoxic chemotherapy to physically and psychologically fragile patients is a huge challenge. There are few data surrounding the administration of chemotherapy to HIV +ve individuals, but is it really sensible in a country with a limited and erratic pharmacopoeia?

The majority of patients with cancer in developing countries present late. Palliative care is cheap, safe and is often the only choice left for the patient. The patients we see do not present early, when the chances of a cure are highest – they present late and so palliative care is 'where we are at' for the majority of Malawians.

The burden of cancer in developing countries is growing but the majority is preventable[30], as the populations are more susceptible to cancers stemming from infectious disease[28] – infection is responsible for 25% of cancer in developing countries[31]. Therefore the priority must be to establish prevention and screening programmes, as well as improving training programmes and maintaining a cancer registry. This approach potentially offers the most valuable and cost effective intervention for reducing the cancer burden[30].

'Do not try to do everything for everybody' [28] – the concept of rationing is as important here as anywhere, especially when the total annual expenditure on health per capita in Malawi[32] is just US$ 64, and the average cost of CHOP chemotherapy per person33 is US$3,118.

There is indeed a need to increase awareness of the need for improved cancer care in Africa in order to effect a co-ordinated, well resourced, sustainable and safe cancer service in Malawi; but Malawi is not yet able to provide this, and until it can a cytotoxic chemotherapy programme is not morally justifiable.

Commentary

Dr. T. Latham

The ability to treat and cure many patients with lymphoma has been one of the success stories of the last 50 years. Unarguably, it is relatively easy and inexpensive to administer chemotherapy drugs with the expectation that tumour regression will occur rapidly at least in the short term. However the progressive improvements in overall survival rates seen since the introduction of combination chemotherapy in the 1960s and 70s have largely been due to improvements in supportive care and the development of organised cancer services rather than advances in chemotherapy drugs[34]. It is uncertainty about the quality of outcomes in the absence of such supportive care that leads to the difficulty in decision making.

There are two parallel questions being argued here. The easier question for academic debate is whether a chemotherapy service should be developed in Malawi given current resources. Clearly the current situation where patients might be sent abroad at great expense or receive treatment according to what drugs are currently in the hospital is inconsistent and inefficient. A *consistent strategy* for cancer care can be developed at local or national level however limited the resources, and would create a framework for gradual introduction of a wider range of treatment options and outcomes monitoring as resources allow. The question of priorities is harder to resolve. It would certainly be feasible to develop facilities to safely give well established regimens of moderate intensity such as CHOP to a limited number of patients. However there is a case that resources should first be concentrated on improving pathology and supportive care services which are prerequisites for giving chemotherapy safely and rationally. Another alternative approach would be to concentrate on lower intensity regimens that could be administered more widely. Although less intense treatments may have been shown in a developed world context to achieve inferior remission rates, it is quite likely that the increase in treatment related mortality because of poorer general healthcare conditions may reduce overall survival for the intensive treatments. Furthermore, more lives might be saved by giving an inferior treatment to a greater number of people. There is no single correct solution to this dilemma, and so it is important to collect holistic outcome data which includes economic, quality of life and availability indicators.

The harder dilemma for the clinician is what should be done for the individual patient in the absence of such a service. Arguments that the patient will necessarily die without chemotherapy and so should be given the chance, however small, are difficult to refute; however the quality of life of a poor-prognosis patient may be made worse with little real hope of benefit. In terms of classical medical ethics, the conflict here is between the duties of beneficence and non-maleficence. While cure is obviously the most beneficial outcome, the duty of beneficence can and often must be satisfied in other ways such as relief of suffering. The avoidance of harm is the other side of the equation. Even with optimal supportive care, chemotherapy patients must often become worse before they get better. I think that there is a difference between suffering because of disease and suffering as a result of medical treatment side effects, especially for patients with little understanding of modern healthcare. Nevertheless, the probability of a good outcome in a well-selected good prognosis patient, even in the absence of good supportive care, may well be better than for many cancer patients treated with intensive treatments in the developed world[35]. As always, the final decision remains one that must be taken according the conscience of the individual clinician and the wishes of the patient.

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