POINT/COUNTERPOINT

Suggestions for topics suitable for these Point/Counterpoint debates should be addressed to Colin G. Orton, Professor Emeritus, Wayne State University, Detroit: ortonc@comcast.net. Persons participating in Point/Counterpoint discussions are selected for their knowledge and communicative skill. Their positions for or against a proposition may or may not reflect their personal opinions or the positions of their employers.

Radiotherapy is an appropriate treatment to consider for patients infected with the Ebola virus

Wilfred F. Ngwa, Ph.D.
Department of Radiation Oncology, Harvard Medical School, Boston, Massachusetts 02115
(Tel: 617-525-7131; E-mail: wngwa@lroc.harvard.edu)

Roland Teboh, Ph.D.
Department of Radiation Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland 21231
(Tel: 410-502-1751; E-mail: troland1@jhmi.edu)

Colin G. Orton, Ph.D., Moderator

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OVERVIEW

The Ebola virus has been spreading rapidly in West African countries and the medical profession has been urgently seeking ways to treat patients infected with the disease in order to stop it spreading further. The predicament in Africa is desperate and totally unproven treatments are being tried on patients. It has been proposed that even some forms of radiotherapy (RT) should be considered, and this is the suggestion debated in this month's Point/Counterpoint.

Arguing for the Proposition is Wilfred F. Ngwa, Ph.D. Dr. Ngwa earned his B.S. in Physics/Computer Science from the University of Buea, Cameroon and his M.S. and Ph.D. degrees in Physics/Biophysics from the University of Leipzig, Germany. He then had postdoctoral training in Medical Physics at M.D. Anderson Cancer Center Orlando, FL and the joint Department of Radiation Oncology at Brigham and Women's Hospital and Dana Farber Cancer Institute, Boston, MA. He is currently Faculty Medical Physicist in Harvard Medical School and the University of Massachusetts, Lowell. He also codirects a Radiation Oncology Global Health Initiative Towards Elimination of Cancer Disparities. Dr. Ngwa's major research interest is nanoparticle-aided radiotherapy for the treatment of prostate cancer, lung cancer, and retinal diseases, for which he has several grants.

Arguing against the Proposition is Roland Teboh, Ph.D. Dr. Teboh is an ABR board-certified Radiation Oncology Physicist and Head of Service, CyberKnife and Stereotactic Radiosurgery/Radiotherapy (SRS/SRT), Division of Medical Physics at the Johns Hopkins University School of Medicine, where he also completed his Fellowship. He earned a B.Sc. (Hons) in Physics from the University of Buea, Cameroon, an M.S. in Physics from Michigan Technological University, Houghton, MI, and a Ph.D. specializing in Medical Physics from the University of Texas Health Science Center at San Antonio. He is a two-time recipient of the ACMP Young Investigator Award and has authored/coauthored over 50 articles and abstracts in peer-reviewed journals.

FOR THE PROPOSITION: Wilfred F. Ngwa, Ph.D.

Opening Statement

The 2014 Ebola outbreak has captured the world's attention, as healthcare professionals and scientists work ardently to find vaccines and treatments for this swiftly spreading, high mortality disease. Ebola infection is characterized by low normal white blood cell count, fever, persistent fatigue or weakness, easy bleeding/bruising, joint/bone pain, etc., and ultimately potential death from severe bleeding, shock,

or organ failure.[1] These characteristics are reminiscent of blood cancers like leukemia and lymphomas whose treatment often involves radiotherapy. Also, the Ebola virus belongs to the virus family Filoviridae, which has been shown to be one of the most radiosensitive of viruses.[2] Following infection, the virus also replicates at a usually high rate, which would render infected cells unusually radiosensitive. This high radiosensitivity, and precedent for using radiotherapy in the treatment of blood cancers with similar disease characteristics, provides a strong rationale for investigating radiotherapy as a treatment approach for patients infected with the Ebola virus.

One potential radiotherapy treatment approach that could be considered is total body irradiation (TBI). TBI is currently used with increasing sophistication to treat leukemia and other blood cancers (destroying abnormal/infected blood cells) and/or for suppressing a patient's immune system in preparation for stem cell transplantation.[3,4]

From what is currently known about the Ebola virus, its primary targets in the early phase of infections are the blood leukocytes that provide innate immunity.[1,5] The virus swiftly renders the innate immune system ineffective, particularly inhibiting dendritic cells from initiating an adaptive immune response and hence disrupting a crucial connection between the patient's innate and adaptive immune system needed to develop antibodies to fight the disease. To make matters worse, the virus then "hijacks" the helpless leukocytes to help propagate the infection by (1) helping transport the virus throughout the body to vital parts such as the lymph nodes, spleen, brain, and liver. It is the ultimate failure of such parts, such as the liver due to chronic hepatocyte infection, that can cause death; (2) releasing a cocktail of proinflammatory cytokines that destroy the vascular endothelium, causing bleeding, and excessive activation of the blood clotting cascade that causes death in some patients.[6]

Cognizant of this, TBI, or a low dose adaptation of it, presents as a viable disruptive approach for consideration for the treatment of Ebola patients. The example of using TBI in the treatment of leukemia and other blood cancers[3,4,7] serves as a precedent for such a disruptive approach. And, as with leukemia treatment, such an approach could be combined with adjuvant administration/transfusion of a fresh supply of blood stem cells and/or chemotherapy. Actually, bleeding problems for Ebola patients are currently addressed by blood transfusions, so this also has precedent.

Another radiotherapy approach that could be considered is radioimmunotherapy (RIT). A recent study shows promise for using this approach to eradicate HIV virus infected cells.[8] Radioimmunotherapy could be considered as an option for targeting the Ebola envelope glycoprotein, which is also a main target of drugs currently under investigation.[9]

AGAINST THE PROPOSITION: Roland Teboh, Ph.D.

Opening Statement

Renewed interest in the quest for a cure for the Ebola virus disease (EVD) is due in part to the recent outbreak originating in the West African countries of Guinea, Sierra Leone, and Liberia. This is a global public health concern that desperately needs a viable treatment modality but, regretfully, I have to argue against consideration of RT as a solution to EVD mainly because the side effects will limit the dose that can be used such that it cannot be curative.

Furthermore, there is a dire need for RT in so-called low and middle income countries (LMICs) such as this region of the world. The need for RT is for the treatment of cancer, not Ebola. The projected estimate is that cancer incidence will rise to 9.3×10^6 new cases per year by 2020 in LMICs, constituting two-thirds of all new cases in the world. Disproportionately, the distribution of teletherapy machines based on a 2010 report shows that the average number of such machines per million people was 1.99 for the whole world: 8.6 for high-income countries, 1.6 for upper middle-income countries, 0.71 for lower-middle-income countries, and 0.21 for low-income countries.[10] Because more than 50% of all cancer patients receive some form of RT as part of their care,[11] lack of RT resources means that a diagnosis of cancer in this part of the world usually leads to distress and a painful death. The need for RT is thus critical and, if no action is taken now, a severe crisis looms that will be of far greater consequence than that currently due to EVD. A consideration of RT as a solution to EVD is an unnecessary digression and could trivialize a true need, especially in the eyes of the authorities that matter, including local governments, business leaders, philanthropists, etc.

Finally, several promising solutions are under development. For example, the World Health Organization has approved the use of an untested drug ZMapp (Mapp Biopharmaceutical, Inc., San Diego, CA) for EVD patients.[12] This is the so-called "secret serum" that was administered to two US aid workers who fell sick with EVD while working in Liberia.[13] There are several other efforts reported in the literature with experimental drugs that have been proven effective in animal models.[14] It does appear that lack of funds and global interest is what has prevented the next step, namely, testing the efficacy and safety in humans.[14] Therefore the immediate focus should be to mobilize world resources to support current scientific efforts so that a safe drug for EVD can be developed.

To conclude, RT has a true and urgent need in LMICs. It is for cancer care and not EVD.

Rebuttal: Wilfred F. Ngwa, Ph.D.

Dr. Teboh makes an excellent point about safety. Beyond taking the right precautions, the development of vaccines and treatments for Ebola will reduce this concern. Human trials of vaccines for Ebola are being conducted.[15] However, while investigations for these vaccines are being expedited toward preventing infection, including among healthcare workers, different treatment options also need to be investigated in parallel.

This brings us back to the question of whether radiotherapy merits consideration as a treatment option. Dr. Teboh prematurely dismisses such consideration. His main argument is that considering radiotherapy for this is a digression from cancer care. However, for the Ebola patient who may

potentially have this as the only treatment option, it will not be a digression as it could be a life saved. Also, it is always better to have as many tools/treatment options as possible to combat a disease. Now is a good time to investigate other potential treatment options in parallel with ZMapp, especially given the growing urgency to find a cure.[16] Moreover, we know that sometimes a combination of treatments could work more effectively for some diseases, depending on the stage of presentation. Finally, the point on digression discusses Ebola as if it is only a problem/concern for low and middle income countries, where resources needed to treat cancer are in short supply. However, other countries are, rightfully, also concerned because of the potential for bioterrorism.[2,17]

In conclusion, low-dose TBI (Ref. 18) (with relatively fewer side effects and risks than high-dose TBI), using Co-60 units, for example, whose sources have decayed too much to be useful for conventional radiotherapy (to address Dr. Teboh's argument about digression from cancer care), radioimmunotherapy,[8] or adaptations of these approaches, should be considered in developing a radiotherapy approach for treating Ebola. My opening statement on precedent, expected high radiosensitivity of Ebola-infected cells and *in-vivo* evidence in using such radiotherapy approaches to treat other virus-infected cells,[8,19] provide a compelling rationale for such consideration.

Rebuttal: Roland Teboh, Ph.D.

Dr. Ngwa suggested TBI and radioimmunotherapy (RIT) as possible RT modalities that can be considered for EVD. I believe that the problems associated with these treatments make this unlikely.

As TBI involves irradiation of all cells, in theory, differential radiosensitivity is crucial if the goal is to eradicate residual EVD cells with curative intent. My colleague stated that the EVD virus is highly radiosensitive albeit relative to other viruses. Studies show that viral inactivation requires high doses, up to kGy,[20] therefore it is likely that high doses are required for EVD response. Toxicity then becomes a major concern, keeping in mind that the LD50, the total-body dose for 50% lethality, is about 4.5 Gy.[21] Furthermore, radiosensitivity is not the only factor. For example, TBI, once considered for Ewing's sarcoma, a highly radiosensitive cancer, has been shown to cause toxicity without disease control.[22]

Given that TBI is largely used as part of the preparatory regimen for hematopoietic stem cell transplant (HSCT), one could envisage a low-dose version of TBI playing the same role toward EVD. One must emphasize, however, that for HSCT, TBI is mainly used as a means to immunosuppress the host so as to prevent rejection of the donor marrow cells, not as a cure. Also, experience with HSCT for viral infections like HIV is inconclusive in that the first patient reported to have been functionally cured of HIV, received a bone marrow transplant from an HIV-resistant donor.[23] Also, two HIV patients who were treated with HSCT and initially seemed to have been cured of HIV, had the infection return.[24]

There is no question that monoclonal antibodies (mAbs) in the 1970s revolutionized antibody therapeutics[25,26] and gives hope today that RIT could be used to treat infections like HIV (Refs. 27 and 28) and, potentially, EVD. A major disadvantage, however, is the cost, since the high specificity means that more than one antibody might be needed to target microorganisms with high antigenic variation, which is possible with EVD given its five distinct species: BDBV, EBOV, RESTV, SUDV, TAFV.[29]

In all, the cost/benefit ratio has to be considered especially given competing alternatives such as ZMapp. Indeed, the first two patients administered ZMapp are now EVD free.[30] Although it is unclear if ZMapp helped, this is welcoming news and encourages further assessment.

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