

Bevacizumab in Advanced Cervical Cancer: Issues and Challenges for Low- and Middle-Income Countries

abstract

Bevacizumab became the first molecular antibody to show survival benefit in advanced cervical cancer. In the GOG-0240 (Paclitaxel and Cisplatin or Topotecan With or Without Bevacizumab in Treating Patients With Stage IVB, Recurrent, or Persistent Cervical Cancer) trial, it improved overall survival by a significant 3.7 months over platinum doublet chemotherapy alone. However, this discovery is not likely to improve the status of global cervical cancer because more than 85% of patients with cervical cancer live in low- and middle-income countries and cannot afford bevacizumab. This commentary looks at the options by which this drug can be made more affordable and cost-effective for patients in low- and middle-income countries. We also discuss other important questions related to its affordability and cost issues such as the optimal number of cycles and personalizing the treatment. Finally, we emphasize that although the unaffordability of bevacizumab in cervical cancer seems to be a very important issue, the best cost-effective strategy against cervical cancer is prevention with screening and vaccination.

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Bishal Gyawali
Mahesh Iddawela

Bishal Gyawali, Nobel Hospital, Kathmandu, Nepal; and **Mahesh Iddawela**, Monash University, Clayton, Victoria, Australia.

Corresponding author: Bishal Gyawali, MD, Department of Clinical Oncology and Chemotherapy, Nagoya University Hospital, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan; Twitter: @oncology_bg; e-mail: bg.bishalgyawali@gmail.com.

Cisplatin-paclitaxel combination therapy has remained the standard of care for advanced cervical cancer for many years.¹ This combination improves survival by only a few months compared with placebo, and we have been unable to make any progress in treating this disease. The demonstration of survival advantage with bevacizumab, therefore, is a milestone—the first positive trial in many years and the first antibody therapy to be approved for cervical cancer. The GOG-0240 (Paclitaxel and Cisplatin or Topotecan With or Without Bevacizumab in Treating Patients With Stage IVB, Recurrent, or Persistent Cervical Cancer) trial showed a significant survival benefit of 3.7 months (17.0 v 13.3 months; hazard ratio, 0.71; $P = .004$) with the use of bevacizumab plus chemotherapy compared with chemotherapy alone. Adding bevacizumab also significantly improved the response rates compared with chemotherapy alone (48% v 36%; $P = .008$).² This finding has the potential to significantly improve the prognosis of nearly a half million patients with cervical cancer across the globe annually.

In this commentary, we discuss some important issues regarding the applicability of this important study to the majority of patients with cervical cancer who live in low- and middle-income countries (LMICs).

Is Bevacizumab Really Expensive?

Whether a particular commodity is expensive depends on the purchasing capacity of the consumers. More than 85% of cervical cancers occur in LMICs,³ with a mortality rate more than three times that in developed countries.⁴ A study showed that treatment with bevacizumab will incur an expense of nearly \$21,083 per month of added life and \$24,597 per quality-adjusted life month.⁵ To put this into perspective, the gross national income (GNI) per capita of an LMIC is \$2,037 according to World Bank data. It is quite paradoxical that a month of treatment costs more than ten times the annual GNI per capita. Cervical cancer is a disease we stage using the International Federation of Gynecology and Obstetrics (FIGO) staging system, which does not include computed tomography (CT) or magnetic resonance imaging (MRI) because CT and MRI are out of reach of many patients in LMICs.⁶ Surely, patients who cannot afford CT or MRI could never afford bevacizumab.

Furthermore, the high cost of bevacizumab and the resulting financial toxicity to the patient, society, and the entire health care system has been a matter of much concern, even for high-income countries (HICs).⁷ This high cost has rendered

bevacizumab cost-ineffective, even for cancers in which it has shown survival gains such as colorectal cancer^{8,9} and cervical cancer.^{5,10} When bevacizumab is considered cost-ineffective for HICs, no one would argue that it is unaffordable and beyond the reach of most patients with cervical cancer living in LMICs. It is striking to note that even if the price of bevacizumab were reduced by 75%, it would still cost \$6,737 per quality-adjusted life month,⁵ which is still three times the annual per capita GNI of someone living in an LMIC. Thus, despite the promising results from the GOG-0240 trial, the global cervical cancer survival rate in the post-bevacizumab era is not likely to improve appreciably.

Can Bevacizumab Be Made Affordable for Patients Living in LMICs?

At the moment, this is the most pressing question bothering both oncologists and patients living in LMICs, and some solutions have already been proposed. The authors of the GOG-0240 trial acknowledge that bevacizumab is out of reach for people living in LMICs and speculate that it will take many years before this option becomes accessible to them.^{2,11} The major hope lies in the introduction of biosimilars in the future that will reduce the incremental cost-effectiveness ratio significantly.⁵ However, introduction of biosimilars will take considerable time. Furthermore, bevacizumab is considered to be an especially challenging product for producing biosimilars.¹² The biosimilars should then undergo an equivalence study before we can confidently put our trust in them.

Besides waiting for biosimilars, it is high time we demanded that the pharmaceutical industry truthfully acknowledge its corporate social responsibility and provide the drug for free (preferably) or at a large discount to patients living in LMICs. Surely the cost incurred in the development of bevacizumab has already been replenished a thousandfold, given its use against a wide variety of cancers, including glioblastoma and lung, breast, kidney, colorectal, and ovarian cancer, for a long time. Thus, it is not entirely unrealistic to demand free bevacizumab for poor patients living in LMICs in collaboration with other nonprofit organizations. The Glivec International Patient Assistance Program that provides free imatinib to eligible patients living in developing countries serves as a testimony for the feasibility of this approach.¹³

Unfortunately though, this optimism seems unrealistic when looking at recent developments. India, an LMIC in South Asia that has recently been taking proactive steps to combat cancer, has

taken a liberal policy in allowing development of biosimilars of many cancer drugs to promote competition and lower pricing. However, as of May 17, 2016, Roche—the manufacturer of bevacizumab—is known to have sued the Drug Controller General of India in Delhi High Court over the approval of biosimilars of bevacizumab.¹⁴ We, echoing the voices of all oncologists and patients from LMICs, strongly appeal to Roche to instead follow the lead taken by industry members such as GlaxoSmithKline, which has recently announced that it will not patent cancer drugs in LMICs.¹⁵

Dose, Schedule, and Duration of Bevacizumab

The pivotal trial establishing the role of bevacizumab in cervical cancer used bevacizumab at a dose of 15 mg/kg once every 3 weeks.² The earlier phase II trial decided upon this dose and schedule on the basis of the ease of combining it with chemotherapy agents.¹⁶ Thus, there is no strong rationale for strictly adhering to this dose and schedule. A cost-effectiveness analysis of bevacizumab in cervical cancer has shown that the cost of chemotherapy decreased from \$49,831 to \$26,472 when bevacizumab dose was reduced to 7.5 mg/kg from 15 mg/kg.¹⁰ Although this is still quite expensive for patients in LMICs, it does represent a significant cost reduction. Clinical studies comparing various doses and schedules of bevacizumab would settle this question, but such trials are unlikely to be funded by the industry. Hence, LMICs—with assistance from international nonprofit organizations and institutions—should take the initiative and conduct and/or participate in the trials comparing different doses and schedules of bevacizumab for cervical cancer. That trial in itself would provide an opportunity for many patients with cancer to receive bevacizumab and validate the efficacy of lower doses of bevacizumab. HICs would be equally interested in such studies because bevacizumab has been shown to be cost-ineffective, even for HICs, at the current price and dosing levels. Thus, collaboration between LMICs and HICs is highly desired in the conduct of such trials and is of global importance. We have already shown that it is much cheaper and easier to conduct clinical trials in LMICs compared with HICs, although some unique challenges need to be addressed.¹⁷

Another important issue with bevacizumab is the uncertainty regarding the optimal number of cycles for administration. In the GOG-0240 trial, it was given once every 21 days until disease progression. The median number of cycles was seven (range, zero to 36), the most common reason for

stopping treatment being disease progression.² For patients and physicians working in LMICs, it is important to ascertain whether the administration of a limited number of cycles of bevacizumab, say two or three, is equally efficacious. This question is important because we sometimes encounter patients who can afford only one or two cycles of bevacizumab, but not more. We have no guidelines regarding whether using two cycles of bevacizumab is better than not using it at all. Because anti-VEGF stress induces tumors to develop alternative mechanisms of angiogenesis-independent tumor vasculature, there are concerns that bevacizumab withdrawal could cause the tumor to become more aggressive.¹⁸ The authors of a recent cost-effectiveness analysis of bevacizumab in cervical cancer reported that “if a payer is able or willing to pay \$21,083 for one more additional life month before death, then chemotherapy plus bevacizumab should be administered.”^{5(p493)} But we are concerned that for a patient who can afford only \$21,083 but not more, one cycle of bevacizumab might not provide an additional month of life, and at worst, it could even make the disease more aggressive. A subgroup analysis of the GOG-0240 trial according to the number of bevacizumab cycles (eg, one to three v more than three) would provide some useful insights.

Can We Personalize Treatment With Bevacizumab?

In the era of such expensive treatment, personalizing treatment is the most cost-effective method available. Unfortunately, we do not yet have validated predictive factors for bevacizumab. However, using Moore criteria in the GOG-0240 trial, the hazard ratios for death in low-risk, mid-risk, and high-risk patients were 0.96, 0.673, and 0.536, respectively. The lack of statistically significant benefit among low-risk patients means that bevacizumab should be reserved for mid- and high-risk patients only.¹¹ In addition, preliminary reports suggest the decrease in circulating tumor cells could be used as a predictor and prognostic biomarker.¹⁹ Further validation of this finding would help realize the dream of personalizing bevacizumab treatment in cervical cancer.

Are LMICs Going to Lose the Battle Against Cervical Cancer Without Bevacizumab?

Although bevacizumab is the most recent and attractive option, the most effective weapon we have in the battle against cervical cancer is prevention. More than 99% of cervical cancers are

associated with human papillomavirus (HPV) infection, and effective vaccines are now available that can help make this disease preventable. Although nine-valent vaccines are now available for HICs, if the LMICs can incorporate quadrivalent or bivalent vaccines into their routine vaccination program, that would prevent more than 70% of cervical cancer cases.²⁰ With support from the GAVI Alliance, HPV vaccination in developing countries is slowly gaining coverage and the poorest countries now have access to a sustainable supply of HPV vaccines for as little as \$4.50 per dose compared with \$100 for the same in HICs.²¹ Therefore, the governments of LMICs should be focused on increasing the coverage of HPV vaccination rather than the affordability of bevacizumab. Because smoking is another important risk factor for cervical cancer, another focus for the governments of LMICs should be to conduct effective anti-smoking campaigns. If we can control HPV infection through vaccination and smoking control campaigns, we can control a significant percentage of advanced cervical cancer cases.

Cervical cancer passes through sequential precancerous stages that allow us to intervene for early detection. It is known that invasive cervical malignancy typically develops in those who are unscreened or underscreened.²² Thus, early detection represents a very important area of intervention. Fortunately, several studies regarding cost-effective modalities for screening have provided options useful for low-resource settings. A single round of HPV testing significantly reduced advanced cervical cancer incidence and mortality in rural India.²³ Screening that uses visual inspection with acetic acid in one or two visits is found to be a cost-effective alternative to three-visit cytology-based screening for resource-limited settings.²⁴ Another important study showed that this type of screening can be conducted effectively by primary health workers and can significantly reduce mortality.²⁵ Thus, effective screening by using cost-effective methods represents the best solution. With concentrated efforts toward vaccination coverage and screening, we can envision a future in which the number of patients that present with advanced-stage cervical cancer can be significantly reduced so that the affordability of bevacizumab becomes less of a social problem.

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Bishal Gyawali

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Mahesh Iddawela

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