Biosimilars in oncology: everybody agrees but nobody uses?

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Summary. Reducing the cost of biologics is an important avenue for addressing financial toxicity in oncology, one of the biggest challenges for health systems. The use of biosimilars, the cheaper alternatives to biologics, is an important strategy to that end. But the enthusiasm of developing biosimilars is meaningless if they get to the market, but they’re not prescribed by the physicians, concerned by unexpected side effects or inferior efficacy. A recent study found no differences between biosimilars and erythropoietin stimulating agents originators in the composite outcome including all-cause mortality, blood transfusion and major cardiovascular events. Such studies are important to allay the concerns of physicians and patients regarding the use of biosimilars. Physician and patient education, backed by clinical guidelines and patient advocacy groups, are the keys to improving the uptake of biosimilars in clinical practice.

Financial toxicity is emerging as one of the biggest challenges of modern cancer care due to the high cost of new cancer drugs. This skyrocketing cost of modern cancer drugs has pushed cancer care beyond the realms of affordability for the majority of cancer patients. The majority of these newer expensive agents are biologics. Indeed, biologics account for the highest oncology-related drug expenditures in outpatient clinics despite being relatively fewer in number. Thus, reducing the cost of biologics remains an important avenue for addressing financial toxicity in oncology and the use of biosimilars, the cheaper alternatives to biologics, represents an important strategy to that end.

The European Medicines Agency (EMA) defines a biosimilar medicine as a medicinal product, which is similar to a biological medicine that has already been authorized (the "biological reference medicine"). Europe has been leading the movement to use biosimilars with regulatory approval process in place as early as 2005. Indeed, while EU approved its first biosimilar (epoetin alfa and filgrastim) in 2007, the US did so (filgrastim) only in 2015. It is noteworthy that the first few biosimilars were of drugs used in supportive care of cancer, an area frequently overlooked in the discussion of financial toxicity. Indeed, biosimilar erythropoietin stimulating agents (ESAs) costs 25-30% less than the branded epoetin alfa and thus improve both the accessibility and affordability of this drug used in the management of chemotherapy induced anemia.

However, the tale of biosimilars in oncology is twisted. The development and approval of biosimilars is a bigger challenge. The whole enthusiasm of developing biosimilars is meaningless if a biosimilar gets to market but isn’t prescribed by the physicians. A certain amount of caution is understandable and necessary because unlike generics, a biosimilar has modifications of original compound. That’s also why a biosimilar, unlike a generic, has to undergo trials and validations to demonstrate bioequivalence to the original product before it gets approved. However, there are challenges even with the trials of biosimilars because physicians don’t want to enroll their patients just in case the biosimilar proves inferior. Another concern is the emergence of sometimes unexpected side effects with biosimilars. For example, the association of pure red cell aplasia with an erythropoietin biosimilar led to fears about incorporating biosimilars into practice easily. Hence, in order to appease the concerns regarding efficacy as well as safety of biosimilars, real world evidence (RWE) becomes crucial. Encouraging data from RWE helps build confidence among physicians in prescribing biosimilars.

Biosimilari in oncologia: tutti sono d’accordo, ma nessuno li usa?

Riassunto. Ridurre il costo dei biologici è un’importante opportunità per affrontare il problema della tossicità finanziaria in oncologia, una delle questioni più rilevanti per i sistemi sanitari. Fare ricorso ai biosimilari, le alternative meno costose ai biologici, è una strategia importante per raggiungere lo scopo. Ma l’entusiasmo provato nel riuscire a sviluppare questi prodotti resta privo di significato se non si traduce in una maggiore prescrizione da parte dei medici, preoccupati dalla possibile insorgenza di reazioni avverse o di minore efficacia. Uno studio recente ha dimostrato l’assenza di differenze tra gli Erythropoietin Stimulating Agents biosimilari e gli originatori, rispetto agli esiti di mortalità per tutte le cause, ricorso a trasfusioni ed eventi cardiovascolari maggiori. Simili studi sono importanti per rispondere alle preoccupazioni di medici e pazienti per quanto riguarda l’uso dei biosimilari. L’educazione del medico e quella del paziente, sostenute da linee-guida cliniche e da gruppi di patrocinio dei diritti dei pazienti, sono la chiave per migliorare la diffusione dei biosimilari nella pratica clinica.
In this context, a recent study published by Italian colleagues comparing the effectiveness and safety of biosimilars versus originators of ESAs is very topical and important. In a population-based cohort from Lazio, Italy, the authors analyzed 13470 incident ESA users in the setting of chronic kidney disease (n=8161) or oncology (n=5309) between 2012-2014 using a registry. Thankfully and unsurprisingly, the study found no differences between biosimilars and originators in the composite outcome including all-cause mortality, blood transfusion and major cardiovascular events. In the oncology setting, the originators in fact suggested a possible detriment versus biosimilars with regards to all-cause mortality (HR for biosimilars versus originators 0.82, 0.70-0.97) although the composite outcome didn’t show such differences. The authors appropriately conducted a sensitivity analysis in a subgroup of oncology patients and found that the cause of death was cancer in 41.9% patients on originator versus 35.9% patients on biosimilars. The authors also conducted genetic matched analysis (a method of multivariate matching) and found similar results including possible detriment with originators in cancer patients. Although possible detriment in all-cause mortality with ESAs have been demonstrated in previous trials of originators, the main take-home here rather is that the biosimilars were safe and effective. If anything, the biosimilars are more protective than the originators but this is a hypothesis to be explored in future studies.

While all the caveats of RWE do apply, this is a well-conducted study and the authors have done their best to control as many confounders as possible. Although some important confounders such as iron supplementation, body-mass index etc. haven’t been controlled and 6 months of follow-up might not be enough to pick-up late signals, this study goes a long way to encourage and promote the use of ESA biosimilars in routine practice.

The credibility of RWE especially lies in the consistencies of findings. In this context, it is important to review another RWE study in the same setting published last year, again from Italian colleagues. Among 1003 incident ESA users from CKD and cancer set-
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cancer patients in Nepal were being prescribed sunitinib off-label simply because it was available for free. Thus, at the other end of the biosimilar uptake spectrum, lies the overuse of biosimilars due to relatively cheaper price. It should be remembered here that ESAs (originators or biosimilars) are not frequently needed in cancer care. The objective in using ESAs in cancer patients is to avoid transfusion and related effects. ESAs themselves come with a price, increasing the risk of thrombosis and possibility of reducing survival and time to tumor progression. Knee-jerk use of transfusion or ESAs must be avoided based solely on an arbitrary hemoglobin cut-off. For a cancer patient, it mightn’t matter much whether his Hb is 10 or 11 if it doesn’t lead to any symptomatic changes. Indeed, we are never treating anemia, we are always treating a cancer patient who has anemia and for that individual, anemia may or may not be his/her concern or the cause of symptoms. Furthermore, major guidelines don’t recommend the use of ESAs in cancer patients who are not on active therapy or receiving non-myeloablative therapy or receiving myeloablative therapy with curative intent. The whole patient and his/her disease status must, therefore, be considered before institution of ESA therapies. Indeed, in cancer medicine, it is as important to practice “avoiding wisely” as it is to “choosing wisely”.

In cases where ESA therapy is judged to outweigh the risks, it becomes the responsibility of a physician to recommend a biosimilar given the reassuring evidence. A study has shown that 100% conversion to biosimilars in a hypothetical population of 100,000 patients would allow an additional 12,913 rituximab, 5171 bevacizumab or 4908 trastuzumab treatments under financial toxicities of cancer treatment, clinical trial methods, and supportive treatments of cancer.

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**References**


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Bishal Gyawali, MD, is a medical oncologist with experience in cancer care in both low-income and high-income countries. After graduating medical school in Nepal with seven gold medals, he is now in the final year of his postgraduate training and PhD in medical oncology in Japan as a MEXT (Ministry of Education, Culture, Sports, Science, and Technology) scholar. His original and opinion articles have been published in top oncology journals. He also provides critical commentary on oncology updates of every month at his blogs on the ecancer website (http://ecancer.org/advanced-search.php?Keyword=bishalgbtn-Search = 1). He is a reviewer for various oncology journals, an editorial adviser to the BMJ and a Journal of Global Oncology Editorial Fellow for 2017. His areas of clinical and research interests include evidence-based oncology practice, global oncology, cancer policy, cancer management in resource-limited settings, financial toxicities of cancer treatment, clinical trial methods, and supportive treatments of cancer.

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