Biosimilars in Oncology: From Development to Clinical Practice

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Biologics play an integral role in the treatment of cancer not only for their therapeutic effects and ability to improve outcomes, but also as supportive care agents. Biologics are more complex to manufacture and take longer to bring to market. Because biologics are considerably more costly than small-molecule drugs, their use has placed an increasing economic demand on healthcare systems worldwide. Biosimilars are designed to be highly similar to existing branded biologics, but because biologics cannot be exactly copied, biosimilars should not be referred to as generic, exact versions of the innovator biologic. Biosimilars have the potential to increase access and provide lower cost options for cancer care as patent protection for some of the most widely used biologics begins to expire. Regulatory requirements for biosimilars are evolving, as are global harmonization and/or standardization strategies that can facilitate their robust clinical development. This review highlights critical factors involved with the integration of biosimilars into oncology treatment paradigms and practices. Clinicians will likely seek out practice guidelines and position statements from established scientific societies to help evaluate key information regarding biosimilars, such as efficacy, safety, comparability, and interchangeability with the reference biologic. Automatic substitution, nomenclature, extrapolation of clinical data from one indication to another, as well as parameters for ongoing pharmacovigilance are evolving considerations. Education of physicians and other healthcare providers, payers, and patients about biosimilars may facilitate informed decision making, promote acceptance of biosimilars into clinical practice, increase accessibility, and expedite associated health and economic benefits.
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Biologics have become an important part of cancer treatment regimens.[1] As a result, major guidance documents in oncology now incorporate biologics into recommended treatment regimens. The addition of monoclonal antibodies such as bevacizumab and trastuzumab into the antineoplastic therapy armamentarium has helped to significantly improve key outcomes including progression-free survival (PFS) and overall survival (OS) compared with chemotherapy alone.[2] In contrast to cytotoxic chemotherapeutics, biologics have allowed cancer treatment to be more specific and targeted. Bevacizumab, for example, is designed to target vascular endothelial growth factor, whereas trastuzumab is designed to selectively inhibit the human epidermal growth factor 2 (HER2) receptor.[3,4] When used in combination with established chemotherapy regimens in patients with metastatic colorectal cancer, bevacizumab significantly improves OS, PFS, and overall response rate compared with chemotherapy alone.[3] Similarly trastuzumab used in combination with standard chemotherapy (doxorubicin + cyclophosphamide or paclitaxel) significantly improves key outcomes including time to progression, response rates, and 1-year survival in the subgroup of patients with HER2 overexpressed (+3 by immunohistochemistry) breast cancer.

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Table 1. Comparison of Biosimilars Versus Generic Small-Molecule Drugs[8,18]

	Biosimilars	Generic Drugs
Synthesis	Produced in living systems, generally using recombinant DNA technology	Produced through standard chemical synthesis
Identity with reference product	Designed and engineered to be similar, but cannot be 100% identical	Typically identical to the reference product
Structural features	Many layers of structure including primary, secondary, tertiary, quaternary, as well as post-translational modification	Typically simple molecular structure
Stability	Monitoring of manufacturing conditions required to maintain stability	Typically stable molecules
Immunogenicity	Immunologic testing and pharmacovigilance used to monitor for immunogenicity	Typically nonimmunogenic
Interchangeability	*Guidance pending* May or may not be interchangeable with the reference product – pending limitations on existing scientific methodologies	Interchangeable with the reference product, assuming similar purity and bioequivalence has been demonstrated
Automatic substitution	*Guidance pending* May or may not necessarily be automatically substituted with the reference product	Generally automatic substitution for the reference product is allowed
Nomenclature	International naming system for biosimilars is varied, US regulations for biosimilar naming are under development	Generally has the same INN as the reference product

Abbreviation: INN, International Nonproprietary Name.

Trastuzumab has provided the first truly targeted therapy for women with this type of cancer.[4] In the supportive care setting, erythropoietin and filgrastim are used to reduce the frequency of important cancer treatment–related events such as anemia and febrile neutropenia.[1,5–7]

Biologics are manufactured from living organisms and take longer to develop and bring to market relative to conventional therapies.[2] "Generic" versions of biologics cannot be manufactured due to the complexity of the proteins themselves (Table 1).[8] Biologics, including humanized monoclonal antibodies, are composed of large and structurally complex molecules. They require extensive immunogenic testing and pharmacovigilance strategies to monitor for the potential of evoking an immune (antibody) response (immunogenicity) (Table 1). Because biologic drugs cannot be exactly copied, the term "biosimilars" is used to describe biologics that are developed to be highly similar to existing, branded biologics.[9] The high level of similarity to the reference product is defined in terms of physicochemical characteristics, efficacy (including antitumor activity), and safety, based on the results of a comparability exercise that is outlined by regulatory authorities.[10,11] The benefits of biologics come at a cost. Often, they are more expensive than small-molecule therapies.[12] Some of the more widely used biologics in oncology are subject to patent expiration in the near future. Recently, the US Food and Drug Administration (FDA) provided initial draft guidance on a development and approval pathway for biosimilars in the United States, whereas regulatory guidelines have been developed and several biosimilars introduced in the European Union (EU) and elsewhere worldwide.[10,13] Clearly delineating biosimilars from the innovator product may help patients and physicians distinguish one product from another, and also maintain strict standards for ongoing pharmacovigilance reporting.[14]

In this review, the considerations associated with the integration of biosimilars into clinical practices in oncology, including the regulatory framework, need for global standards and harmonization, the role of clinical guidance documents, interchangeability and automatic substitution of biosimilars for existing branded biologics, safety monitoring, and questions relating to the overall acceptance of biosimilars by the oncology community are examined. All of these factors will need to come together for the successful integration of biosimilars into oncology practice (Figure 1).