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Biosimilars and cancer treatment of older patients☆

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ABSTRACT

Biosimilar monoclonal antibodies are being developed globally to meet clinical demand in oncology and potentially provide greater access to biologic therapies for patients with cancer, including older patients. In this supplement, we present an overview of the development, approval requirements, and characteristics of biosimilar monoclonal antibodies that may help practicing oncologists and other healthcare providers to acquire familiarity with this new group of therapeutic biologic agents. Furthermore, we review and discuss some of the challenges and potential strategies for the management of older patients with cancer, who represent an increasing population in many countries.

Supplement Introduction

The introduction of targeted therapy with monoclonal antibodies (mAbs) has improved efficacy of treatment and prognosis for cancer patients with solid tumors or hematologic malignancies in the past decade [1]. Older patients with cancer also derive benefit from biologic therapies, although they may require more careful assessment and treatment selection compared with younger patients, depending on overall performance status and potential comorbidities [2–4]. Biosimilar mAbs are now being developed globally to meet clinical demand in oncology and potentially provide greater access to biologic therapies for patients with cancer [1].

In this supplement, we present an overview of the development, approval requirements, and characteristics of biosimilar mAbs that may help practicing oncologists and other healthcare providers to acquire familiarity with this new group of therapeutic biologic agents. Further, in the second section, we review and discuss some of the challenges faced in the management of older patients with cancer, who

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represent an increasing population in many countries. A consensus is emerging on the need to tailor treatment for older patients; chronologic age per se should not dictate the course of action. Optimization of patient assessments and current treatment algorithms and access to efficacious and safe therapies as well as implementation of well-designed clinical trials may help provide effective treatment options for older patients with cancer [5–7].

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First Section — Basics of Biosimilars

Introduction

Biologic drugs encompass a wide range of products such as hematopoietic growth factors (e.g. erythropoietin, filgrastim), recombinant hormones (e.g. growth hormone), and targeted monoclonal antibodies (mAbs) (e.g. anti-HER2 mAb trastuzumab, anti-CD20 mAb rituximab, and anti-epidermal growth factor receptor mAbs cetuximab and panitumumab) [1]. Biosimilars are biologic drugs designed to be highly similar to the reference biologic product, also known as the originator [2–6]. In contrast to generic drugs, which can be identical to their reference product, most biosimilars are highly complex molecules produced in vitro by recombinant DNA technology. Further, biosimilar mAbs undergo post-translational modifications (e.g., glycosylation) and assembly in multi-chain, immunoglobulin structures [7]. Minor differences may thus be present in clinically inactive components of biosimilar products [6]. However, by definition, a biosimilar is "a biologic product that is highly similar to a reference biologic product, notwithstanding minor differences in inactive components," and for which there are "no clinically meaningful differences in safety, purity, or potency of the product" (H. R. 3590-686. Title VII. Subtitle A- BPCI Act. §7002) [5, 6].

The concept of a "similar biological medicinal product" was first introduced in the European pharmaceutical legislation in 2003 and the legal basis for the biosimilar approval pathway was adopted in 2004, coming into effect in 2005 [1]. Regulatory guidance documents for the definition, approval, and the use of biosimilars were initially released in Europe by the European Medicines Agency (EMA) in 2005 with later updates [2,3]. In 2009, the World Health Organization (WHO) published its "Guidelines for the evaluation of similar biotherapeutic products (SBPs)" [4]. In 2010, the Patient Protection and Affordable Care Act was signed into law and created a pathway for the approval of biosimilars in the United States [5]. Guidance documents were subsequently released in the United States by the Food and Drug Administration (FDA) in 2012 and 2015 [6, 7]. These regulatory approval pathways outline the biosimilar paradigm, which requires a sponsor to demonstrate biosimilarity between the proposed product and a reference product, and to demonstrate that "there are no clinically meaningful differences between the biologic product and the reference product" [5, 6, 8].

In this review we outline current requirements for approval of biosimilars, discuss the rationale for the development of biosimilar mAbs in oncology, and address their potential impact in the management of older patients with cancer.

Evaluation and Approval Requirements for Biosimilars

According to current regulatory guidance from the EMA and the FDA, a stepwise process involving pre-clinical and clinical evaluations is required to determine biosimilarity to a reference product, including demonstration of comparable safety and efficacy (Fig. 1) [2, 6]. Pre-clinical, comparative studies of potential biosimilars rely on physicochemical characterization and on in vitro bioassays for the evaluation of structural and functional properties (e.g. peptide mapping, in vitro cytotoxicity assays). In vivo animal and human studies are conducted to evaluate pharmacokinetic (PK) characteristics, safety, immunogenicity, and pharmacodynamic (PD) effects of biosimilars. Comparative PK and PD analyses may be performed in the same study, allowing determination of biosimilarity in PK profiles and in vivo effects on preselected biomarkers or target cells (e.g. patterns of B cell depletion by CD20-targeted mAbs). PD studies should include determination of the relevance of available PD biomarkers for the stated mechanism of action, time of the PD marker onset relative to dosing, and sensitivity of the PD marker to differences between a biosimilar and its reference product as well as correlations between changes in PD markers and clinical outcomes [6, 8].

Potential biosimilars are further evaluated in head-to-head comparative clinical trials designed to assess biosimilarity between a biologic drug and its reference product in patient populations sensitive to potential differences in clinical

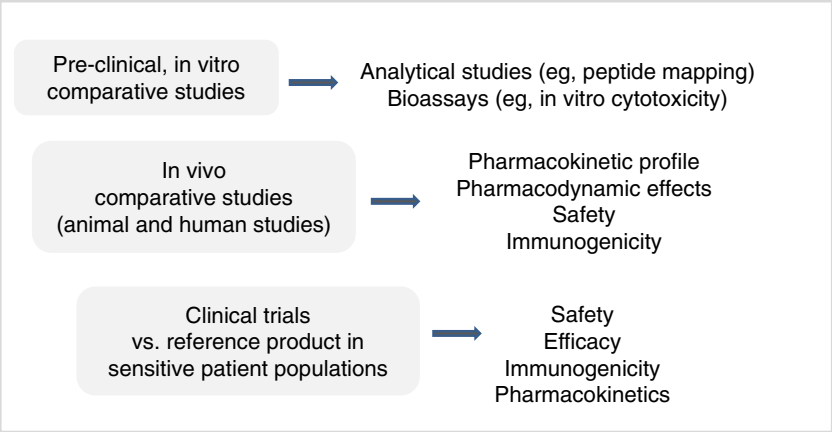

Fig. 1 – Stepwise evaluation of biosimilars [2, 6, 8].

activity, including safety, tolerability, immunogenicity, and efficacy [6]. Clinical trial endpoints should be selected to maximize detection of potential differences between the biosimilar and the reference product rather than to redefine overall clinical benefit, which was already established in clinical studies conducted with the reference biologic [2,6]. Accordingly, sample size and duration of comparative studies should allow assessment of any potential difference, including any newly emerging safety signals [6]. Endpoints for clinical immunogenicity studies should include measurements of immune response to the biosimilar and to the reference product, such as specific antibody responses (e.g., titer, time of development, persistence, disappearance, and neutralizing activity) and cytokine levels [6]. In some cases, appropriately selected pharmacodynamic endpoints known to be correlated with clinical outcomes in the study populations may allow for more accurate comparative studies of biosimilars and their reference products than clinical endpoints. Concomitant evaluation of multiple pharmacodynamics endpoints may further enhance the sensitivity of the comparative clinical studies undertaken for biosimilars [6]. Introduction of novel, exploratory endpoints tailored to specific biologic drugs and clinical settings may also be considered in building the body of evidence required to establish biosimilarity in pivotal clinical trials [6,9,10].

The FDA has recently approved the first biologic product through the biosimilar regulatory pathway, Zarxio™ (Sandoz/Novartis, Basel, Switzerland), which is a biosimilar version of the hematopoietic growth factor filgrastim. In this case, primary endpoints in the pivotal study EP06-109 conducted in 28 healthy volunteers were biosimilarity in pharmacokinetics and pharmacodynamics (absolute neutrophil count). The secondary endpoints of this study included safety, immunogenicity, and local tolerance. Further, primary endpoint of the pivotal clinical study EP06-302 conducted in 218 patients with breast cancer treated with myelosuppressive chemotherapy was non-inferiority in mean duration of severe neutropenia in cycle 1. Mean patient age in this trial was 49 years (range, 23–76 years). Overall, only 30 (approximately 9%) of the 334 female breast cancer patients included in the biosimilar filgrastim pivotal studies EP06-301 and EP06-302 were >65 years of age [11]. Furthermore, the FDA has also recently accepted applications for other biosimilars.

Rationale for the Development of Biosimilars in Oncology

MAbs directed to key targets expressed by cancer cells, such as trastuzumab, cetuximab, panitumumab, bevacizumab, rituximab, and ofatumumab have been approved to treat patients with HER-2+ breast cancer, head and neck cancer, non-squamous non-small-cell lung cancer, colorectal cancer, or hematologic malignancies (e.g. lymphoma and chronic lymphocytic leukemia), respectively, and have led to more effective standard-of-care treatments for these patient populations [1]. However, future availability of essential therapeutic agents in oncology may be compromised by the loss of patent protection and market exclusivity projected to occur within the next 3–4 years for a number of these mAbs [1]. There have been a number of shortages reported globally in the past few years for non-branded, generic but essential oncologic drugs, including 5-fluorouracil, bleomycin, cytarabine, doxorubicin, and fludarabine as well as antibiotics, analgesics, and parenteral nutrition products, which have affected availability of treatment options, patient safety, and overall healthcare costs [12].

Biosimilars need be differentiated from “intended copies” or “non-comparable versions” of biologic drugs, which are products now being marketed in some countries in Central/South America and in Asia [13,14]. These products may not have been developed according to strict WHO standards and thus may not have been developed through the stepwise, comparative, pre-clinical and clinical studies required to demonstrate biosimilarity to the reference product [4,15]. In contrast, biosimilars approved by health authorities (e.g. EMA or the FDA) and produced according to current industry standards [16] are expected to be high-quality biologics that may sustain and increase access to biologic therapies for patients with cancer. An Office of Pharmaceutical Quality has been recently opened by the FDA within the Center for Drug Evaluation and Research, which is expected to establish benchmarks for

the determination of manufacturers' compliance with Good Manufacturing Practices (GMPs) intended to ensure effective oversight of manufacturing operations throughout the life cycle of a pharmaceutical product. In the case of drugs approved for use by the FDA but not produced in compliance with current GMPs, the severity of the violations identified generally determines the nature and extent of the FDA regulatory actions. In rare cases, the FDA may ask a company to stop distribution or manufacturing of a pharmaceutical product if it is found in serious violation because it does not meet its labeled specifications and may endanger safety and effective treatment of patients [16].

Further, to provide state-of-the-art information on biosimilar development and approval, the FDA has initiated a dedicated source called the Purple Book or "Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations," which is easily accessible through its website [17]. Such lists are updated periodically and will include biosimilars upon approval. Further sources of information on biologics and biosimilars are provided here by the FDA both for healthcare providers and consumers.

Emerging Biosimilar mAbs and Potential Impact in Cancer Care

In response to the challenges that may affect availability of key biologics frequently used for the treatment of patients with cancer, a number of biosimilar mAbs are being developed according to current FDA/EMA/WHO regulatory guidance and expectations and GMP standards by well-established manufacturers, including biosimilars to trastuzumab, rituximab, and cetuximab [1, 15, 16]. For the biosimilars approved through the EMA or FDA regulatory pathways, post-marketing implementation of appropriate pharmacovigilance programs and reporting of adverse drug reactions by established manufacturers will allow surveillance of their use in daily clinical practice [18–20]. This is especially important for older patients because comorbid conditions and a reduction in organ reserves can alter drug tolerance. In addition, recent pharmacoeconomic analyses suggest that biosimilars may have a substantial impact on the range of treatment options available to clinicians, patients, and payers in many settings [14,21–24]. For example, according to a recent model, cost-savings deriving from the use of biosimilars in supportive care in France, Germany, Italy, the United Kingdom, and Spain would allow increased access to anticancer biologics without additional expenditures [23]. A broad access to biosimilar anticancer mAbs may further help in addressing financial issues experienced by patients and their families or financial toxicity, which has been defined, on a graded scale, as the potential impact of healthcare-related costs on standard of living, quality of life, treatment selection and adherence, and ultimately treatment outcomes [25]. In a global community conscious of healthcare costs and driven to implement cost-effective treatment plans with preservation of access to high quality of care, biosimilars may be a lower cost alternative to off-patent biologic therapies and provide efficiencies to healthcare systems. Furthermore, achievement of a suitable balance between a broader adoption of biosimilar products and the concomitant development of novel, innovative products for potential inclusion in combination regimens frequently used in oncology, may represent an effective strategy within an evolving therapeutic landscape.

In conclusion, the introduction of high-quality biosimilars may provide access to biologic therapies to a greater number of patients with cancer, who are seeking safe and effective treatment options, including older patients with cancer.

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Second Section — Evolving Cancer Treatment for Older Patients: Biosimilars

Introduction

Cancer affects a substantial proportion of older adults, and it represents one of the leading causes of death in this population. Based on the demographic changes currently occurring in developed countries, a further increase in the number of cancer patients aged 70–75 years or more is expected for the next decades [1–5]. A number of challenges are frequently encountered in daily clinical practice by oncologists caring for older adults, including the presence of comorbidities (e.g. cardiovascular disease, compromised respiratory or renal function, liver abnormalities, cognitive deficits), a reduced tolerability for treatment-related toxicities, the need for multiple concomitant medications (polypharmacy), a reduced performance status, and a compromised ability to perform daily basic activities as well as limited transportation, social support, and financial resources [6]. These epidemiologic and clinical trends underscore the growing importance of optimizing diagnosis and therapeutic interventions in geriatric oncology to better address the needs of older patients with cancer [2, 6].

Effective geriatric screening and assessments, appropriate referrals, careful selection of treatment options tailored to each patient conditions, access to standard of care and innovative treatments as well as adequate supportive care represent main objectives in the multidisciplinary management of older patients with cancer [1, 2, 5, 7–9].

In this section, we outline the progress made so far in some key areas of geriatric oncology and discuss treatment patterns with targeted biologic therapies and their implications for older patients with cancer, in view of the ongoing development and future availability of biosimilar monoclonal antibodies (mAbs).

Screening and Assessment of the Geriatric Patient with Cancer

The decrease in functional reserves associated with aging, as well as the presence of potential comorbidities and the frequent need for polymedication, render each older patient unique in their status, thus requiring careful screening and assessment at an individual level if cancer is suspected or diagnosed. Accurate assessment of a patient's performance, medical condition, functional reserve, and goals of care is the key to selecting appropriate treatment options, to prevent

overtreatment and the associated toxicities in frail or vulnerable patients and to avoid undertreatment of fit patients simply based on older age [7–14].

To achieve these goals, a substantial number of screening tools have been developed for the assessment of older patients. Five of these tools have been specifically designed for older patients with malignancies: Geriatric 8 (G8) tool, the Oncogeriatric Screen (OGS), the abbreviated Comprehensive Geriatric Assessment (aCGA), the Senior Adult Oncology Program questionnaire (SAOP2), and Gerhematolim [10]. G8 has shown value in predicting chemotherapy-associated toxicity and overall survival (OS) in older patients with solid tumors but not with hematologic malignancies. Conversely, Gerhematolim has demonstrated a high sensitivity (95%) and specificity (87%) in older patients with hematologic malignancies. The aCGA tool contains 15 of the most important items present in the full CGA and has demonstrated a sensitivity of about 50% and specificity of 97% compared with the CGA [10].

Polypharmacy and Clinical Pharmacology Considerations for Older Patients With Cancer

Administration of multiple medications occurs frequently in older patients due to the presence of comorbidities and the need for specific treatments. Other factors contributing to polypharmacy may derive from a lack of coordination between specialists and primary care physicians as well as routine continuation of prior therapies. In the oncology setting, polymedication is often further accentuated by the need to treat adverse drug reactions [15–24].

As the aging process and comorbidities may further interfere with absorption, metabolism, and excretion of drugs and their metabolites, drug administration in older patients should be tailored to their age, goals of care, and physical characteristics (e.g. weight and renal or liver function), carefully planned and continuously monitored to prevent unwanted toxicities and undesired reactions [15, 18, 23].

Periodical re-evaluation of all medications taken by a patient may also contribute to a correct long-term treatment strategy and optimal outcomes [19]. The use of a Medication Appropriateness Index (MAI), as well as of the Beer's or the STOPP criteria (screening tool of older persons' potentially inappropriate prescriptions), may help in this process [15–17]. In a patient assessment it is important to collect detailed information on the use of over-the-counter medications and "natural products" (e.g. herbal remedies not regulated by the health authorities), as potential pharmacologic interactions with other medications or undesired adverse effects may be associated with their use and thus influence treatment decisions or overall outcomes [25,26].

Over- and undertreatment are both potential risks associated with the management of older patients. A reduction in the functional reserves, frailty, and comorbidities may require reductions in the dose intensity or delays in treatment to prevent overtreatment and toxicity. Conversely, appropriate medical treatment should not be withheld from a patient with cancer who is fit and in good general and clinical conditions, simply based on advanced age (e.g. 70–75 years or older) [27–31]. Biologic age trumps chronologic age [32]. Although the presence of comorbidities and the related polypharmacy may represent a challenge for inclusion of some older patients in clinical trials (due to the potential introduction of hard-to-quantify variables) and affect their eligibility for comparative studies of biologic agents including biosimilars, careful patient screening and selection would allow inclusion of older but fit patients.

Access to Biologic Agents and Biosimilars for Older Patients With Cancer

Review of the demographic characteristics of patients included in oncology clinical trials reveals that, generally, very few older patients (aged 70–75 years or older) are enrolled in clinical studies, as they frequently do not meet the specified inclusion criteria, or are treated in settings that have no access or infrastructure to support clinical trials [33–42]. "Ageism," which occurs when older patients are eligible for a clinical trial but are not offered the opportunity to participate, may also significantly contribute to low or no enrollment of this patient population in clinical trials, as exemplified in a case–control study conducted in the breast cancer setting [35]. Importantly, non-inclusion of older patients in cancer trials may deprive them of early access to investigational treatments with greater efficacy or better tolerability compared with available standard treatments.

Once suitable treatment options have been identified for each patient with cancer, individual access to treatment becomes of key importance; however, logistic, financial, and practical issues may build barriers to effective patient management [43]. Appropriate referrals at cancer diagnosis may help patients and their caregivers identify clinical providers and oncologic teams that may effectively deliver high-quality cancer care over the course of the disease. A multidisciplinary and inter-professional approach with integration of the care provided by medical, surgical, and radiation oncologists and by geriatricians and primary care physicians is also necessary to ensure that patients are optimally treated for their cancer and all the potential comorbidities in a synergistic continuum of care.

The ongoing development and future approval of biosimilar anticancer agents is expected to increase patient access to mAbs, such as trastuzumab, rituximab, cetuximab, and panitumumab, in addition to the hematopoietic growth factors frequently used in supportive care [43–45]. These mAbs are currently integrated in standard-of-care regimens for the treatment of early and advanced breast cancer (BC), lymphoma (e.g. diffuse large-B cell lymphoma; DLBCL), chronic lymphocytic leukemia, locally advanced head and neck squamous cell carcinoma, and metastatic colorectal cancer, among other malignancies. They have demonstrated safety and efficacy in the general patient population and in selected cohorts of older patients, mostly evaluated in retrospective analyses or registry studies [28,43,46–51].

Results from a survey conducted among oncologists in the United States and in other countries (i.e. Brazil, Mexico, Russia, and Turkey) have shown that multiple barriers may limit access to HER2-targeted treatment with trastuzumab in the adjuvant, neoadjuvant, and metastatic BC setting [48]. A total of 7994 full-time physicians involved in patient care were invited to participate in this survey, with an overall,

pre-specified goal of 200 responders in the United States, and 75 each in Brazil, Mexico, Russia, and Turkey (N = 500) [48]. Further analysis of these survey results revealed that ~30% of the responders reported not being able to prescribe trastuzumab as needed or having to delay treatment. Such percentage rose to 60% in the United States for difficulties in prescribing trastuzumab for patients with HER2+ metastatic BC [48]. Of note, approximately half of the responding oncologists said that they would increase the use of HER2-targeted mAb therapy in all clinical settings for patients with HER2+ BC with the availability of a trastuzumab biosimilar product [48].

Similarly, in the United States as well as in emerging countries, physicians may encounter barriers in prescribing rituximab for patients with non-Hodgkin lymphoma or chronic lymphocytic leukemia, as reported in a recent survey, conducted among 450 hematologists and oncologists who completed this survey in the United States, Mexico, Turkey, Russia, and Brazil [50]. In addition, in a recent SEER-Medicare cohort analysis of 9333 patients with DLBCL, older than 66 years of age, 49% of the patients had received rituximab in combination with chemotherapy compared with 23% who received only chemotherapy and 5% who received only rituximab. However, 23% of patients did not receive any treatment, particularly those aged 80 years or older (33%) [51].

In conclusion, the future approval and use of biosimilars in many solid and hematologic malignancies may address the evolving needs of patients and physicians, generate efficiencies for healthcare systems, and provide broader access to standard-of-care treatment options for older patients with cancer.

Disclosures and Conflict of Interest Statements

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Author Contributions

Study concept and design: all authors.
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