

The Future of Colorectal Cancer Drugs: From Chemotherapeutic Agents to Biosimilars

What is a Chemotherapeutic Agent?

A chemotherapeutic agent is a drug capable of killing cancerous cells. They refer to antineoplastic drugs used to treat cancer or the combination of these drugs into a cytotoxic (capable of killing cells) standardized treatment regimen. Since cancer is the uncontrolled growth of cells coupled with malignant behaviour (invasion and metastasis), chemotherapeutic agents act by killing cells that divide rapidly, one of the main properties of cancer cells. This means that it also harms cells that divide rapidly under normal circumstances: cells in the bone marrow, digestive tract and hair follicles; this results in the most common side effects of chemotherapy – myelosuppression, which is decreased production of blood cells, mucositis (inflammation of the lining of the digestive tract) and alopecia (hair loss).

Chemotherapeutic drugs affect "younger" tumors (i.e., more differentiated) more effectively, because mechanisms regulating cell growth are usually still preserved. With succeeding generations of tumor cells, differentiation is typically lost, growth becomes less regulated, and tumors become less responsive to most chemotherapeutic agents. Near the center of some solid tumors, cell division has effectively ceased, making them insensitive to chemotherapy. Another problem with solid tumors is the fact that the chemotherapeutic agent often does not reach the core of the tumor. Solutions to this problem include radiation therapy (both brachytherapy and teletherapy) and surgery.

There are five classes of chemotherapeutic drugs: alkylating agents, anti-metabolites, plant alkaloids and terpenoids (including vinca alkaloids, podophyllotoxin, and taxanes), topoisomerase inhibitors, and antitumour antibiotics.

Newer anticancer drugs act directly against abnormal proteins in cancer cells; this is termed targeted therapy and the drugs which commonly target cancer cells are called biologics. In colorectal cancer, three targeted therapies have been developed: bevacizumab, cetuximab, and panitumumab.

What is a “biologic”?

A biologic is a term used to refer to a biologically produced organic molecule that is a drug. Biologics are protein-based drugs obtained from natural sources and, therefore, manufactured from animals, or microorganisms, or through the use of animals, or microorganisms, or by recombinant DNA methods. Biologics are now widely used in the treatment of many diseases, including colorectal cancer. Examples of biologics are monoclonal antibodies (such as bevacizumab, cetuximab, panitumumab in

the treatment of colorectal cancer), hormones, enzymes, cytokines and vaccines.

In Oncology, biologics have added major therapeutic options for the treatment of cancer, including some for which no effective therapies were available, and others where previously existing therapies were clearly inadequate.

What is a “Small Molecule”?

A small molecule drug is a medicinal drug compound having a molecular weight of less than 1000 Daltons, and typically between 300 and 700 Daltons. Small molecules can have a variety of biological functions, serving as cell signaling molecules, as tools in molecular biology, as drugs in medicine and in countless other roles. These compounds can be natural or artificial; they may have a beneficial effect against a disease or may be detrimental.

Most drugs are small molecules, although some drugs can be proteins, e.g. insulin. Many proteins are degraded if administered orally and most often cannot cross the cell membranes. Small molecules are more likely to be absorbed, although some of them are only absorbed after oral administration if given as prodrugs. Many dietary supplements are small molecules (but not herbal extracts such as ginkgo).

Differences Between Biologics and Small Molecules

Many small molecule drugs can be taken orally, and tend to work in the body within cells. Since biologics are significantly larger in size, they are typically injected and interact within the body in the bloodstream or on the surfaces of cells, rather than within the cells. In contrast, small molecule drugs are typically composed of only 20 to 100 atoms. Small biologics, such as hormones, are typically composed of 200 to 3000 atoms, while large biologics, such as antibodies, are typically composed of 5000 to 50,000 atoms. To give a sense of size, same-scale computer models of three drugs — aspirin (a small molecule), somatropin (human growth hormone), and Herceptin (an antibody used in the treatment of breast cancer) — are presented below with an example of the relative complexity: The molecules are to scale and the objects are not, but the objects (bike, car, private jet) indicate relative size and complexity of these molecules.

Manufacturing processes for biologics differ greatly from the manufacturing processes for small molecule drugs. Small molecule drugs are generally synthesized using chemical reactions. Biologics, by comparison, are typically produced within specially engineered cells. Small molecules are well-characterized, and can be easily purified and analyzed with routine laboratory tests. Biologics — especially larger biologics - tend to be produced as diverse mixtures of molecules that differ very slightly from one another, which make them difficult to characterize. It follows that the properties of the biologic often depend directly on the nature of the manufacturing process. Furthermore, proteins have unique structural organization patterns (referred to as "folding") that affect the way that they

work in the body; even biologics that are chemically the same may have differing biological effects due to differences in the structural folding. An example of this folding effect is the difference between a raw egg and a cooked one: chemically the two are the same, but they are physically and biologically very different.

What is a “Biosimilar”?

A biosimilar is used to describe a biologic product that would be similar to and would enter the market subsequent to an approved innovator biologic, following patent expiry. Other terms used include “biosimilar”, “similar biological medicinal product”, and “follow-on protein products”. The introduction of a biosimilar would rely, in part, on prior information regarding safety and efficacy that is deemed relevant due to the demonstration of similarity to a reference biologic product. A biosimilar is not a “generic” biologic because the approval process and marketed use for a biosimilar differs from that of a generic pharmaceutical. Biosimilars will always require clinical trials and will have unique safety and efficacy profiles when compared to the innovative reference product.

It is important to note that the bio manufacturer does not have access to the originator biologic’s molecular clone and original cell bank, nor to the exact fermentation and purification process. And, nearly undetectable differences in impurities and/or breakdown products are known to have serious health implications. This has created a concern that copies of biologics might perform differently than the original branded version of the drug.

There are challenges associated with producing biosimilars in Canada. The development of a process whereby regulatory decisions on biosimilars would be based on the evaluation of reduced/limited clinical data presents challenges to manufacturers and regulators alike. Safety, quality, and efficacy must be guaranteed despite changes to the manufacturing process, which is inherent in the production of a biosimilar.

The following issues are being explored by the CCAC in an effort to maximize patient safety and choice as they relate to the use of biosimilars in the management and treatment of colorectal cancer:

i. Need For Regulatory Framework

Health Canada has generated a [Guidance Document](#) as opposed to “Regulations” to oversee the development and introduction of biosimilars into the Canadian marketplace. While helpful, guidelines are inherently less rigid than regulations and, therefore, cause for concern as it relates to potentially diminished patient safety and product efficacy.

ii. Approval Process Involving Non-Approved Innovator Products

Health Canada has already permitted the use of Canadian non-approved innovator products (biologics) as a reference product in which to generate and approve a biosimilar in Canada. For example, a biologic that has yet to be approved in Canada, but approved abroad, may serve as a reference product in which to approve a biosimilar in Canada. This may prove problematic in light of the fact that prescribing physicians do not have a wealth of experience with the innovator product and, therefore, unable to gauge patient response. This is a situation unique to Canada for other nations (ie the United States, European Union, Australia/New Zealand, Asia and Latin America) do not permit non-approved products to serve as the reference product for the development of a biosimilar. The first Canadian biosimilar which received market approval in April 2009 (Omnitrope) is derived from a non-approved innovator biologic in Canada, which could potentially set a precedent for the approval of future biosimilars derived from non-approved innovator biologics.

iii. Definition of Similarity Required

Since biosimilars are similar to and not the same as the innovator biologics, Health Canada is producing guidelines/criteria for the definition of “similarity” as it relates to biosimilars, whose interpretation throughout the manufacturing process may, therefore, be subject to a degree of bias, raising the concern of potentially diminished product efficacy. The concepts of similarity and comparability are distinct and must be properly applied to any approval process of a biosimilar product. Manufacturers of innovator products are permitted to make post-approval manufacturing changes to their products based upon a showing of comparability between the two products. This is considered appropriate because innovator manufacturers possess a thorough and robust body of knowledge about the process used to manufacture the original product, which can be applied in support of subsequent modifications to the manufacturing process. In contrast, a biosimilar product would be approved based on an analytical determination that the product is similar to the innovator product. Subsequently, new clinical data will be required to support similarity to an innovator product. Furthermore, a complete analytical comparison with the reference product is necessary to support approval of a biosimilar.

iv. Need For Pre-Clinical Data

The amount of pre-clinical data submitted to secure the market authorization of a biosimilar is limited in comparison to the data submitted in respect of the innovator biologic. What remains constant is the degree of post-market surveillance between the two. To secure a level of comfort, the biosimilar-associated pre-clinical data and end points should be as robust as possible and much like that generated for the innovator product.

v. Pharmacoeconomics vs. Patient Safety/Product Efficacy

The cost of producing biosimilars is approximately 15-30% less than that of the innovator biologic. Assuring patient choice may be problematic for patients who rely on publicly funded biologics, for prescribing physicians may be compelled to prescribe the less expensive product, thereby potentially compromising patient choice, outcomes and safety. Dictation of formulary positioning and pharmacoeconomics should be discouraged if it is at the expense of patient safety and product efficacy.

vi. Post Market Surveillance Required

Since biosimilars would be approved based in part on the prior approval of the innovator product, sponsors might be allowed to submit less data than that of the innovator to support approval of their products. As such, biosimilars manufacturers would have less experience with their products. In order to protect patients from products with less complete data packages, continued assessment of the product after approval is necessary, and biosimilars sponsors should be required to have risk management plans in place to compensate for this gap in data by collecting the additional necessary experiential information during the post-market surveillance.

The European Union has a stringent pharmacovigilance plan (post-market surveillance) in place for the purpose of identifying specific, rare and non-predictable safety-related events. Long term monitoring is mandated for the evaluation of immunogenicity (allergic reactions). Despite Canada's efforts to develop a comprehensive plan in the introduction and management of biosimilars, no stringent pharmacovigilance plan has been identified or proposed.

vii. Product Traceability/Identifiability

Biotechnology-derived products are complex proteins that are extremely difficult for even the innovator to manufacture. Minor changes in the manufacturing process can inadvertently result in significant and possibly dangerous differences to the final product. Therefore, it is critical that products administered to patients be identifiable and traceable back to the manufacturer. Patient safety interests require that adverse events be quickly and accurately correlated with the actual product administered. This correlation is essential to allow for immediate action to recall products when manufacturing processes resulted in a product causing patients to experience adverse events.

The European Union also has a plan in place regarding traceability of biosimilars. The adverse events generated from the use of biosimilars require tracking and traceability and necessitate differentiation from originator product which essentially mandates a proper reporting system to track the variations within the same biosimilar product.

viii. Product Interchangeability Not Permitted

No foreign nation allows for interchangeability between the innovator biologic and biosimilar. Although Canada has declared this same position, it lacks the means of enforcement amongst the various provinces in Canada, thereby, potentially allowing publicly funded drug plans from making these products interchangeable with the innovator biologic. Subsequently, provinces might deviate from Health Canada's recommendation and adopt substitution or bioequivalence between the innovator biologic and the biosimilar. This would, in turn, classify biosimilars as generic chemical molecules which they clearly are not. A regulation is recommended overseeing the public drug plans adopting the equivalent clarity to Health Canada's position that biosimilars will not be interchangeable with innovative biologics in the reimbursement setting.

ix. United States FDA Biosimilars Regulations Encouraged

BioteCanada, a leader in, and national voice for Canada's biotechnology sector, is recommending that the United States' FDA biosimilars Regulations be adopted by Canada, with amendments, which they claim are more rigid than the current Canadian Guidelines in place.

Colorectal Cancer Canada (CCC) has adopted a position relating to the introduction of biosimilars in the Canadian Marketplace. CCC supports the introduction of biosimilars provided colorectal cancer patients who rely on publicly-funded drugs, including biologics, are assured the choice between the innovator biologic and the biosimilar when it comes to accessing the medications that are appropriate for their treatment. It is imperative that continued safety and maximal efficacy be assured. CCC believes that innovative biologics are the key to the future of cancer treatment and, therefore, must be protected to ensure future research and development as well as patient access in Canada.