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Pharmacology of Oral Chemotherapy Agents

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The past few years have been witness to exciting advances in the treatment of patients with cancer. Two trends in particular are of note: the use of chemotherapy that is less generally cytotoxic and more specifically targeted to cancer cells and the administration of oral medications to cure or control cancer.

This article focuses on oral chemotherapy agents that have been approved recently for use in the United States and includes a discussion about what makes them unique in their effects on cancer cells as opposed to healthy cells. Their effects may be a matter of preferential delivery to the anatomical site of the cancer, exploitation of molecular differences between cancer cells and healthy cells, or variation in enzymatic transformation of the drug that tends to spare healthy cells at the expense of cancer cells.

The earliest discoveries in cancer research featured chemotherapy agents. These drugs disrupted the cell cycle in various ways, leading to cell death. Because cancer cell growth is not as controlled as the growth of healthy cells, these therapies would, in theory, affect cancer cells to a greater degree than healthy cells. In reality, the effects on healthy cells were and often are quite toxic, particularly on cells with rapid growth rates. Thus, the typical adverse effect profile includes myelosuppression, alopecia, and mucositis. Recently, advancing knowledge regarding the genetic and molecular intricacies of human cells has allowed researchers to focus more specifically on the differences between healthy and malignant cells and to exploit these differences to target the latter.

How do researchers develop drugs, and what makes a suitable candidate for an oral agent? Substances may be derived from

The abundance of orally formulated chemotherapy agents reflects the expanding role of oral chemotherapy in the care of patients with cancer. Many oral chemotherapy agents have been used for a number of years, and several have been developed recently. Newer agents include the prodrugs capecitabine and temozolomide, the retinoid bexarotene, the immunomodulatory agent thalidomide, the protein kinase inhibitor imatinib, and the epidermal growth factor receptor inhibitors gefitinib and erlotinib. Each agent has unique pharmacologic properties, dosing, and side-effect profiles. This article reviews these agents from a pharmacology perspective.

Key Words: antineoplastic agents, pharmacokinetics, prodrugs, retinoids

natural products such as plants or created anew in the laboratory. Many thousands of molecular entities often are screened during the search for a single promising agent for further investigation. Although sophisticated techniques and instrumentation have improved efficiency greatly, the process still is an arduous and often lengthy one (Swinyard, 1990).

Development of drugs may be based on astute observations of the effects on humans of previously available chemicals. A classic example is the case of mechlorethamine. During World War I, the remarkable effects of chemical warfare in the form of nitrogen mustard gas on blood and bone marrow were observed (Krumbhaar & Krumbhaar, 1919). Eventually, mechlorethamine was approved and made commercially available. To this day, it is known as “nitrogen mustard” and still is used to treat certain malignancies. Whatever the basis of discovery, staggering amounts of data must be collected, from pre-clinical to human benefit and safety data, prior to submission to the U.S. Food and Drug Administration (FDA) for approval.

The advantages of oral drug delivery are

adequately and reliably absorbed into the systemic circulation.

Many drugs are, in fact, prodrugs. A prodrug is a pharmacologically inert compound that is converted to an active agent by metabolic transformation in vivo (Malet-Martino & Martino, 2002). A prodrug is developed with features that favor it over the pharmacologically active component. For example, an active cytotoxic agent may be manipulated to produce a compound that is relatively nontoxic and, therefore, easier to handle and produce. Prodrugs historically have improved the in vivo delivery of a drug when the active component faces obstacles such as poor oral absorption, insolubility, and instability. Double prodrugs, or “pro-prodrugs,” require two metabolic transformations before becoming chemically active

numerous (Borner, Scheithauer, Twelves, Maroun, & Wilke, 2001; Liu, Franssen, Fitch, & Warner, 1997). Oral drugs may be derivations of previously available injected agents or developed as original concepts. During the oral drug development process, challenges that are specific to the route of administration must be overcome (Bardelmeijer, van Tellinghen, Schellens, & Beijnen, 2000; Birner, 2003; Lipinski, 2002; Stenberg, Bergström, Luthman, & Artursson, 2002). Ideally, a drug is stable in a formulation that is suitable for oral use, is palatable, does not irritate the gastrointestinal tract, readily dissolves after ingestion, and is

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