

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Challenges of Oral Chemotherapy

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H&O What is the reason behind the increasing move toward oral chemotherapy?

JS The move toward oral agents is one of the major developments in chemotherapy. The reason for the increasing interest in oral chemotherapy is to do with the fact that the new biologic agents tend to be more active for chronic treatment than for acute treatment, and therefore they need to be developed for chronic exposure. Chronic therapy is common practice in both solid tumor and hematologic oncology. For example, imatinib mesylate (Gleevec, Novartis) must be taken every day; it would be extremely impractical to have only intravenous (IV) administration available. Other signal transduction inhibitors and several antiangiogenesis compounds also need to be given chronically. In general, drugs that interfere with newly identified biologic endpoints will most likely need to be given on a continuous basis. For these types of agents, oral therapy is more convenient for patients, and also more cost effective, avoiding the outpatient clinic, which can be cumbersome and expensive.

H&O Why have drugs mainly been developed as IV agents in the past?

JS There are several reasons for developing agents for IV use. Drug development is associated with many difficulties in the gastrointestinal (GI) tract. The drug must be stable in the stomach, which has a very low pH. In the small intestine, where absorption takes place, the drug must have good dissolution characteristics. Also, the drug must not interfere with other substances in the GI tract, such as food or other drugs.

After dissolution, the drug needs to be taken up by the GI tract. However, a number of defense mechanisms in the epithelial layer of the GI tract make passage and uptake of drugs into the body difficult. Another difficulty

is passage through the liver, the function of which is to extract toxic compounds and detoxify them. Thus there are a number of hurdles for an oral agent before it reaches the systemic circulation. Agents that have been used for many years as IV formulations, such as docetaxel (Taxotere, Aventis) and topotecan (Hycamtin, GlaxoSmith-Kline), are being explored in oral formulations. The main challenge has been that these agents are poorly taken up in the gut.

Another reason why the IV route has predominated is that initially, therapeutic courses were planned for once every 3 weeks. After a cytotoxic drug is administered, it is important to wait until full bone marrow recovery for the next course, which is approximately 3 weeks. For this treatment schedule, having only the IV route available is not a hindrance.

H&O Do the newer biologic agents require similar recovery between courses?

JS For the new biologic drugs, which typically do not show dose-limiting toxicities and have a very different safety profile from traditional chemotherapy agents, these limitations do not apply. There is no need to take a blood sample to confirm that it is safe to proceed with treatment, for example. From a safety point of view, there is no reason why patients cannot take oral agents at home.

H&O What mechanisms in the gut are preventing oral agents from being effective therapy?

JS Many investigators have contributed to the research of why oral agents are not taken up in the gut, and we now know that there is a protective mechanism that physiologically prevents exposure of the body to these drugs when they are given orally. A protein in the epithelial layer of the GI tracts keeps the drug in the lumen.

H&O Is it possible to circumvent this mechanism in order to improve the efficacy of oral agents?

JS There is a range of drugs that can block the function of these proteins for a short period of time. When oral anticancer drugs are given in combination with a drug that inhibits the function of the protective system in the GI tract, known as an absorption enhancer, the anticancer drug is able to cross the epithelial layer, to be taken up in the body and distributed as an IV agent would be.

H&O Could you further describe this mechanism?

JS The research was started in the laboratory in the 1990s. What we know is that there are a number of proteins in the GI tract that belong to the ABC drug transporter family, with the most well known being P-glycoprotein ("P" stands for permeability). This protein is in the GI tract and has affinity for a wide range of natural compounds. Many anticancer drugs are natural compounds and have affinity for this particular protein. Thus, the physiologic presence of P-glycoprotein protects uptake of the drug. Laboratory research found that P-glycoprotein is not produced in a mouse model in which the Mdr1 gene has been knocked out. When an anticancer agent with known affinity for P-glycoprotein is administered orally in a mouse without this protein, there is almost no inhibition of uptake of the agent. Clearly, P-glycoprotein is a protective mechanism.

Knockout mouse models for P-glycoprotein as well as a range of other proteins in the gut have taught us an enormous amount about the physiologic function of these proteins. Now, this knowledge is being applied to clinical research. Studies are showing that when the protein is temporarily blocked, oral drugs are taken up in the body.

H&O Are oral chemotherapeutics as effective as the standard IV formulations?

JS We conducted several phase II studies in which the endpoint was an assessment of the activity of an anticancer drug. Four studies were conducted, 2 in breast cancer (one with oral paclitaxel and one with oral docetaxel), another in second-line non-small-cell lung cancer, and a first-line study in advanced gastric cancer. The response rate, the typical endpoint of a phase II study, showed that the activity with the oral agents was what was expected based on historic data of these drugs as IV agents for these types of patients. Comparing new agents with historic controls is inherently flawed, but it was interesting to note no difference in activity between the 2 populations.

Part of our plans for the not-too-distant future is to conduct a randomized study comparing oral therapy plus the absorption enhancer with standard IV therapy in order to evaluate whether oral therapy is indeed beneficial and safe.

H&O When will this study be conducted?

JS Before this study can be done, it needs a pharmaceutical sponsor. In order to test this concept in gastric cancer or lung cancer, for example, large number of patients needs to be recruited, approximately 300 (150 per arm). Such a study is very costly. The Netherlands Cancer Institute is a not-for-profit institution and we do not have the money or infrastructure available to do this large phase III study without pharmaceutical support.

H&O Has it been difficult to obtain this sponsorship?

JS With so many compounds that can be developed, it is difficult to prioritize oral chemotherapy, and the cost of the proposed trial is very high for a smaller company. There are also many considerations, such as marketing, management, patent, timeline, and cost that need to be taken into account when considering trial sponsorship. These many nonscientific considerations can prolong and sometimes prevent the decision to sponsor a trial.

H&O Have absorption enhancers been developed since this application of them was identified?

JS There is a range of absorption enhancers already available. Cyclosporine-A, a drug that is registered for use in renal transplant patients, who require this agent to prevent rejection of the transplant, is used most often. This agent has been found to be a good inhibitor of P-glycoprotein, and it can be purchased at the local pharmacy.

There are also several interesting compounds under development that can be used for this strategy. One of the best-known compounds is called elacridar (GlaxoSmithKline). This agent has no immunosuppressive effects, which are seen with cyclosporine-A. It would be ideal to have elacridar available for the pivotal clinical trials of oral topotecan or paclitaxel, for example.

H&O Would certain types of cancer be more susceptible to oral chemotherapy than to IV chemotherapy?

JS We do not yet know, but the concept is very interesting. Many cancers metastasize to the liver. For some drugs, such as paclitaxel, the concentration in the liver after oral administration is much higher than when the same dose is given intravenously. It may be that certain diseases, such as breast cancer with liver metastases, respond better to oral administration than to IV administration. However, there is not yet any data to confirm this theory.

Suggested Reading

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