Irinotecan: A New Agent Comes of Age

In 1966 the plant alkaloid camptothecin was isolated and identified as an agent with promising anticancer properties. Insolubility, however, was an initial impediment to the clinical development of this agent. Phase I studies of the sodium salt of camptothecin, reported in the early 1970s, showed impressive antitumor activity, but also showed severe and unpredictable toxicities. As a result, camptothecin was effectively shelved for a decade and a half, until the identification of topoisomerase I as the target for camptothecin renewed interest in its clinical development.

Just over a decade ago, researchers at a Japanese company known best for its yogurt-based breakfast drinks and its professional baseball team, reported that the eleventh in a series of semi-synthetic, soluble derivatives of camptothecin, (CPT-11, in company shorthand) was demonstrating important activity in a number of refractory tumor models. The patients treated in early phase I trials included a number with refractory colorectal cancer, and some of these individuals experienced clinically meaningful antitumor responses. This finding led to an international effort to define and develop irinotecan as a treatment for fluorouracil-resistant colorectal cancer.

In some respects the development of irinotecan served as a new model for anticancer drug development. Rarely if ever before had there been such a well-coordinated global effort from such an early clinical stage in drug development, and never had a new drug development strategy been focused not on the newly diagnosed, “fresh” patient, but rather on the patient with previously treated, chemotherapy-refractory disease.

Since 1996, irinotecan, used as a second line agent, has been part of the standard management of metastatic colorectal cancer. Newer data from studies in both Europe and North America, summarized in an article that follows, [1] have now established the role for first line irinotecan-fluorouracil combinations in the management of metastatic colorectal cancer. The question of the role of irinotecan-based combinations in the adjuvant setting is being actively explored. Also, as reviewed by Rothenberg [2] in this issue of The Oncologist, the role of irinotecan in tumors other than colorectal cancer is now being actively explored. Clinical trials of irinotecan or irinotecan-based combinations in patients with other gastrointestinal cancers, including esophageal, gastric, and pancreatic cancers, have shown promising initial results. Non-small cell and small cell lung cancers have also shown responsiveness to irinotecan-based combinations. Irinotecan-based treatments are also showing promise in cervical and ovarian cancers.

Where are we going from here? Clearly the role of irinotecan in cancers other than colorectal will require further definition. Furthermore, as the number of active agents available for the treatment of cancers increases, the need for molecular markers to identify a priori which agents will have the greatest chance of success in an individual patient will become ever more important. Thus far, such markers have remained elusive for irinotecan, but extensive efforts in this area continue. As irinotecan takes its place in the standard array of cancer treatments, newer agents are entering the clinical arena. Combinations of irinotecan with these new agents may offer further potential for improved treatments. Only through continued efforts to design and complete clinical trials of these new combinations will we be able to continue to advance the field forward. Our current gains, while modest, represent important progress. However we still have a long way to go and more important work ahead.

REFERENCES

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