Current Role of Irinotecan in the Treatment of Non-Small-Cell Lung Cancer

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The comprehensive review by Dr. Karen Kelly meticulously outlines the rationale for the study of irinotecan in non-small-cell lung cancer (NSCLC), summarizes results of trials of this agent as monotherapy and as a component of doublet and triplet regimens in previously untreated NSCLC patients, and then reviews its role in previously treated NSCLC patients.

Like the taxanes and gemcitabine, irinotecan is certainly an active drug in NSCLC. Unfortunately, however, it appears a therapeutic plateau has been reached in the treatment of advanced NSCLC with these newer active drugs in combination with a platinum compound. Median survivals of approximately 8 months and 1-year survival rates of approximately 35% are now widely reported in multiple phase III trials from a variety of cooperative groups.[1,2]

Strategies for Using Irinotecan

Despite attempts at varying the active agents studied, their schedules of administration, and sequences/doses of component agents, no recent trial has suggested an appreciable move forward with any such approach. To that end, it is difficult to foresee in what setting irinotecan might be routinely advantageous when used in the untreated NSCLC population. However, a burgeoning understanding of the molecular biology of common solid tumors may provide an opportunity for irinotecan and other agents to be used more creatively in this disease.

One such strategy would be to study drug combinations for tumor types in which the leading candidates for successful targeted therapies and irinotecan both have activity. To date, the most promising classes of agents have been either small molecules (eg, erlotinib [OSI-774, Tarceva], gefitinib [ZD1839, Iressa]) or monoclonal antibodies targeting the HER family (trastuzumab [Herceptin], cetuximab [IMC-C225, Erbitux]).

Given the frequency of perturbations in this signaling pathway in common solid tumors and the activity profile of irinotecan, combination trials could be envisioned in NSCLC as well as colorectal, ovarian, and cervical cancers.[3,4] Moreover, preclinical data suggest that epidermal growth factor receptor (EGFR)-tyrosine kinase (TK) inhibitors may be helpful in diseases that have little EGFR expression—for example, small-cell lung cancer (SCLC), in which irinotecan is highly active.[5]

Design of Future Trials

How should these trials be designed to allow expedient interpretable results that could lead to advances in the treatment of common solid tumors? At a minimum, such trials would need to incorporate appropriate correlative studies including pharmacokinetic assays as both irinotecan and the most widely studied EGFR-TK inhibitors are hepatically metabolized and molecular assessments of EGFR pathway activation/inhibition. Since antibodies for phosphorylated (or activated) EGFR are not yet standardized, routine exclusion of patients based on the immunohistochemical profile of EGFR would be unwise.[6]

Trials involving this class of targeted agents would be a logical place to start, but other leads should also be pursued clinically. For example, up-regulation of the nuclear transcription factor NFkB has been detected in cancer cells exposed to irinotecan and could obviate chemotherapy-induced apoptosis.[7] Inhibition of NFkB activation by a proteosome inhibitor such as PS-341 could thus enhance the effects of the cytotoxic agent.

Since randomized phase II designs do not test comparative efficacy profiles and because phase III trials are unwarranted in the absence of provocative results of a pilot trial, we might initially screen for some modicum of activity greater than that seen historically with the chemotherapy agent under
study. When possible, these historical cohorts should consist of patients treated in a similar phase of study, perhaps studied by the same investigators, and with similar clinical characteristics. Such a trial should be undertaken with a two-stage design and powered to detect a minimal level of increased activity that would warrant further study.

**Conclusions**

Irinotecan stands as an active agent for both advanced NSCLC and SCLC. Ongoing phase III trials are attempting to confirm the results of a Japanese trial, and if positive, would likely change the standard of care for extensive-stage SCLC.[8] However, in NSCLC, it will be difficult to identify a unique niche for irinotecan alone or as a component of cytotoxic combinations. Its potential may lie in its suitability for rationally designed combination therapy with novel targeted agents. In this way, it might be successfully employed as the backbone of true therapeutic advances.

**References:**


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