**Editorial**

**Therapeutic Innovation: The Up-Front Window**

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The cure of cancer with chemotherapy has generally required three or more agents used in combination. The cure rate of ALL\(^1\) in children has progressively increased to 80\%, partially as a result of a current total of nine agents (1). The agents individually have definite, albeit limited, activity, but rarely are single agents capable of cure. The good news is that such agents are being discovered and developed in increasing numbers, and an increasing number are proving to be effective in the clinic. For example, there are now some seven agents capable of producing tumor regression in patients with metastatic breast cancer. These provide palliation and possibly a limited increase in survival. The bad news is that new treatments, for example, new Phase II agents, are displaced “outback” by increasing prior chemotherapy. The clinical evaluation of new agents is the gateway to progress in cancer treatment (2, 3).

The first question is “How much antitumor activity is lost by testing new agents after known active chemotherapy has been delivered?” The answer is “a lot.” In breast cancer, for example, doxorubicin, the most active single agent, produces a partial response in 50–55\% of patients when used as the initial chemotherapy for patients with metastatic disease. In patients with prior chemotherapy, the corresponding response rate is 15–20\% (4). With few exceptions, prior chemotherapy with other agents and in other tumors has been similarly adverse. Adjuvant chemotherapy, given months to years before, has been found to adversely affect subsequent chemotherapy (4). The remarkable advances that have occurred in molecular studies of resistance indicate a broad base of cross resistance that further emphasizes the outback problem. Several multidrug-resistant mechanisms have been described. Mutation of the p53 gene may determine the set point for apoptosis for the majority of agents (5–7).

Given the importance of finding effective agents, Gore et al. (8), elsewhere in this issue of Clinical Cancer Research, construct an experimental design that involves the initial treatment of adults with ALL with one to two courses of topotecan, an agent not known to be active in that disease. If topotecan or other agents evaluated using this design turn out to be inactive and/or impart some degree of resistance, the patient may be deprived of standard, potentially curative chemotherapy for ALL. Does the end (the discovery of an effective treatment for future patients) justify the means (decreased therapeutic potential for the individual patient)?

As is often the case, the devil is in the details. Thus, whereas ALL in adults is curative in 30\% of patients, the authors selected high-risk patients for whom the expected cure rate would be 5–10\% (9). Whatever effect this has on the ethical concern, it weakens their experimental design. The response rate to the new Phase II agent is likely to be reduced in such patients. Thus, they have traded the risk of getting a false negative by treating patients outback for the risk of getting a false negative by treating poor-risk patients “up front.”

The likelihood that topotecan would have some activity in ALL is substantial, given its activity in other tumors such as non-small cell lung cancer and myelodysplasia (10).

Is there a precedent for the up-front approach? A somewhat different “up-front window” was pioneered by Sallan in children with ALL (11). The absolute leukemia cell infiltrate in the marrow was determined from the smear and section, and viability was evaluated by dye exclusion. This was performed on the initial marrow. The Phase II agent under study was administered, and 4–7 days later, the marrow and abovementioned analyses were repeated (11). They established the superiority of high-dose methotrexate with leucovorin rescue over standard-dose methotrexate using this in vivo in vitro (window) system. That this was predictive was confirmed by their parallel clinical trial which demonstrated improved survival in the random sample of patients receiving the high-dose methotrexate (11). Using a somewhat similar experimental design, they demonstrated the activity of asparaginase in ALL (12, 13).

It is the rate of tumor regression that is measured in the Sallan window. There is abundant evidence in clinical and preclinical models that the initial rate of response correlates closely with the subsequent magnitude and duration of response and survival.

Another up-front therapeutic window approach is contained in the neoadjuvant or induction chemotherapy strategy. Neoadjuvant chemotherapy was first formulated (14, 15) and applied to advanced head and neck cancer and osteosarcoma in the 1970s and early 1980s (16, 17). The major objectives of neoadjuvant chemotherapy were to reduce a primary tumor in size to increase the potential for cure by local treatment and/or to decrease the need for radical local procedures; to address the micrometastatic tumor as early as possible, thus decreasing the risk of mutation to drug resistance (18); and finally, as with the Sallan window, to determine the responsiveness of the tumor to chemotherapy by an in vivo assay. This can be evaluated by a change in tumor size and, importantly, by a pathology study of the tumor before and immediately after chemotherapy (14–16). The neoadjuvant approach was controversial, and ethical questions were raised, particularly with respect to the delay in local treatment, that is, surgery and/or radiotherapy, which was known to be curative in a limited but definite proportion of these patients. Now, after 20 years, it is clear that neoadjuvant chemotherapy has improved the quality of life, particularly by reducing the frequency and magnitude of radical procedures.
such as laryngectomy, leg amputation, and cystectomy (17). With the exception of stage IIIA non-small cell lung cancer (19), there is no clear evidence that the cure rate has been increased. There is, on the other hand, no evidence that this version of the up-front window has diminished the cure rate.

Breast cancer is a common epithelial solid tumor in which there are many agents that have definite, albeit limited, activity. Traditionally, these are used up front in patients with metastatic disease. How many active agents were missed, that is, discarded as negative, as a result of the outback experimental design? This problem was addressed in a Cancer and Leukemia Group B study in which patients with newly diagnosed metastatic breast cancer were randomly allocated to receive six standard courses of CMF in the control arm or 1–2 months of treatment with Phase II agent that was new or untried in breast cancer followed by 6 months of CMF. There was no significant difference between the experimental and control arms in terms of time to progression or overall survival (20). Derivative designs that differ in detail but are similar in principle are under study.

In short, the treatment, including particularly the definitive treatment of cancer, has depended upon innovation with respect to experimental design.

The authors are technically correct in concluding that topotecan is active in this setting. This is based on 1 complete response in 14 patients and a lesser or no effect in the remaining patients.

The application of molecular biology techniques to the clinic for measuring minimal residual tumor and determining the prognosis and/or response to specific therapies will increasingly contribute to the efficiency and effectiveness of such trials. The authors performed several such studies including the following:

(a) Pharmacokinetic studies to determine whether the blood levels achieved were in the range required for in vitro activity. Increasingly, such pharmacokinetic studies should guide the investigator in terms of dosing and in the analysis and interpretation of Phase I or II studies.

(b) topo I in leukemia cells. There is evidence that a high topo I content is associated with an increased response to topo I inhibitors, such as topotecan. They did not find such a correlation. Indeed, the patient who achieved a complete response did not have an increase in topo I levels.

(c) Antiapoptosis gene BcL2. Preclinical studies suggested that cells containing low levels of BcL2 are more sensitive to topo I inhibitors. High levels of the antiapoptosis gene product BcL2 should be associated with diminished apoptosis and thus would be expressed as drug resistance. Indeed, the authors find that the response to topotecan correlated with low levels of BcL2.

None of the abovementioned studies was statistically significant, mainly because of the small sample size. However, our capacity to measure surrogate end points such as minimal residual tumor will increasingly affect our ability to predict and evaluate response to treatment.

Gore et al. (8) conclude that topotecan has definite, but limited, activity in patients with ALL. Their experience is difficult to interpret because they chose high-risk patients. Thus, it is possible that the agent might have greater activity against a representative sample of adults with ALL. This minimal degree of activity might be of interest if topotecan were nonmyelosuppressive, or if there were compelling evidence that selected patients, on the basis of molecular findings such as BcL2 mentioned above, might have a higher response rate. It certainly should not replace the standard treatment for ALL.

I was asked to review this paper not only for clinical and scientific content, but also for its experimental design and ethical perspective (does the end justify the means?).

The authors provide evidence that their up-front therapy with topotecan did not compromise the results of standard treatment. The clinical and cytogenetic heterogeneity of their small sample size make the study hypothesis generating, that is, provide therapeutic and research leads, but conclusions in terms of therapy are not possible.

"The physician, above all, must do no harm." Actually, Hippocrates didn’t say it quite that categorically. Sir William Osler, who also lived at a time when there was preciously little established therapy, asserted the axiom. Think of where we would be today if the “no harm” axiom prevailed. Surgery, radiotherapy, and chemotherapy: all are invasive; all are harmful; indeed, all may be associated with mortality. The harm and the risk must be balanced against the gain, popularly known as cost effective analysis. We would still be taking warm baths and massages on the island of Cos if we allowed the “do no harm” axiom to hold, that is, to be an absolute.

Can the end ever justify the means?

In a sense, all prospective studies define the end point and use the means for getting there that include protocol-prescribed treatment. We must assure, as did Gore et al. (8), that our safeguards are in place, such as institutional review boards to assure patient safety, science review mechanisms to assure that the question being asked is important and will be answered by the study, and, above all, meaningful informed consent. As with the “do no harm” axiom, the “end justifies the means” axiom could stultify Phase II studies, gateway studies essential to progress in cancer therapeutics.

There are two higher axioms.

The first is the inevitability of change. Innovation is the engine of change. Innovation that may challenge tradition and the establishment must be encouraged within the above guidelines. Yesterday’s research is today’s established treatment, and today’s research will be tomorrow’s established treatment.

The second absolute, also alluded to by Hippocrates, is the integrity of the physician-patient relationship. The physician’s primary concern should be the health and well-being of his patient. We must assure that research is conducted in the context of that relationship.

References

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