

Tubulin/Microtubules: Still a Promising Target for New Chemotherapeutic Agents

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Most investigators would agree that the ideal chemotherapeutic agent should be 1) directed at a validated target; 2) potent, preferably active at nanomolar or subnanomolar concentrations; 3) schedule independent, even active in noncycling cells; 4) active against drug-resistant cells; and 5) less toxic or ideally not toxic to normal cells. In this issue of the Journal, Leoni et al. (1) suggest that indanocine, a synthetic antimetabolic indanone, possesses all of these properties. Further studies will be needed to prove this convincingly, but even if indanocine is not the ideal compound, one may eventually be found or synthesized.

The antimetabolic drugs include a diverse group of compounds, most of which are natural products, whose varied mechanisms of action result in a common end point: mitotic arrest (2,3). The majority of these agents induce mitotic arrest by interacting with tubulin, and the simplest classification divides these agents into those that depolymerize tubulin and those that stabilize tubulin polymers. Depolymerizing agents are further subclassified into those that interact with the vinca binding site and those that target the colchicine site, a group that includes the indanones. Agents that polymerize tubulin include the taxanes, the epothilones, discodermolide, and the sarcodyctin/eleutherobin class of compounds (2-5).

The target for these agents is tubulin, the basic subunit of microtubules and one of the most highly conserved proteins in evolution (6,7). As a group, these agents have been so successful in the treatment of cancer that no one would dispute that tubulin is a valid target. Indeed, given the widespread activity of the taxanes and the utility of the vincas, it could be argued that tubulin represents the single best target identified to date (8). This should not be surprising, since the majority of known antimetabolic agents are natural products, or derivatives thereof, and have been obtained from many classes of organisms, marine and terrestrial, from Cyanobacteria to mammals. One could argue that tubulin, as a target, has been validated time and again by "Mother Nature" (2).

But should we be excited about "yet another" tubulin agent? The answer in our opinion is unequivocally yes. Agents that target tubulin are effective in a broad range of malignancies. While it could be argued that another vinca site agent may not be needed (although any of several new vinca site agents may invalidate this argument), the clinical efficacy of a colchicine site agent has not been adequately evaluated. Although, like the vincas, these agents depolymerize tubulin, an expectation that they will be different is not unreasonable, given the available evidence demonstrating significant differences, especially in clinical practice, among the various vinca alkaloids (vincristine, vinblastine, and vinorelbine). Indeed, it would not be surprising to find a colchicine site agent as different from a vinca as a taxane.

Agents, such as those described by Leoni et al. (1), that can overcome known mechanisms of drug resistance are even more attractive. However, one must be careful to distinguish retained sensitivity from collateral sensitivity. In the former, a mechanism of resistance to A fails to confer drug tolerance to B,

whereas, in the latter, acquisition of a mechanism of resistance to A is accompanied by increased sensitivity to B. In the case of indanocine, the evidence suggests the former, even though in three cell lines increased sensitivity was noted. These cell lines had undergone drug selections and, unlike the transfectants, most likely had other genetic alterations. Thus, we think it prudent to restrain conclusions regarding its activity in drug-resistant cells.

The study also raises the issue of target diversity. Is tubulin indanocine's only target or does it have additional targets? The possibility of alternate targets is raised by the authors to explain their observations that indanocine "induces apoptotic cell death in stationary-phase cells." But we must ask whether the existence of additional targets must be hypothesized to resolve this observation. In other words, are tubulin agents active only against dividing cells that can traverse through mitosis? We believe that invoking a secondary target may not be necessary. As shown by the authors and by numerous others before them, tubulin agents result in marked cytoskeletal disorganization. Given the importance of the cytoskeleton in cellular organization, intracellular transport, and signal transduction (9), it would not be surprising to find that these agents could be cytotoxic to cells in G₁ phase. This need not be at odds with the general belief that these agents are schedule dependent.

Finally, the issue of selectivity is an important one that is widely recognized as desirable. A drug that preferentially or exclusively targets cancer cells, sparing normal cells, would be ideal. For indanocine, further evidence needs to be collected, but it appears likely to us that it will be toxic to normal cells, just as is the case for all of the other agents that target tubulin.

As the new millennium dawns and we wait to see the success of the harvest of this era of "novel drugs" designed for "novel targets," we would be well advised not to overlook what has worked before. While a truly novel target might appear more attractive, we should not ignore drugs directed at "old targets." As the study by Leoni et al. demonstrates, our understanding of this class of agents is still very primitive and the diversity of drugs awaiting discovery likely beyond our imagination. We should take a clue from nature as to the importance of tubulin as a target and not rest until we have pursued all of the leads provided to us. We would be foolish to do otherwise.

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