Letters to the Editor


Letter

In their paper on apoptosis and topotecan sensitivity, Caserini et al. (1) highlight an important aspect of Topo I inhibitor effect on the cancer cell, i.e., its ability to undergo apoptosis following drug-target interaction. The antiproliferative activity of the Topo I inhibitors seems to be different from their apoptotic induction potential. Indeed, this difference may have significant bearing on how one assesses the in vivo efficacy of these drugs.

The camptothecin derivatives topotecan and irinotecan are rapidly becoming established as significant additions to therapeutic strategy in adult solid tumors. The cytotoxicity of camptothecin is mediated through Topo I inhibition and is maximal during the S phase of the cell cycle (2). However, Topo I enzyme inhibition by itself is probably not sufficient to result in cell kill. Cellular events, both upstream and downstream, have the ability to modify the lethal effects of Topo I inhibitors.

Cell cycle progression, following DNA damage that is subsequent to Topo I inhibition, can be arrested at several checkpoints. The regulation of these checkpoints has a major role in determining the sensitivity of the cancer cell to anticancer drugs. In the absence of a functional, wild-type p53, cells progress through G1. The next checkpoint for assessing the suitability of the cell to progress through to mitosis is at the S and G2 phases of the cell cycle. A key regulator of cell cycle is the p34cdc2/cyclin B, the activation of which triggers G2-M transition. Topo I-mediated DNA damage may inhibit activation of this kinase, resulting in G2 arrest (3). This may explain the decrease in G1 and increase in G2 phases in the A2780/CP cell line, which has relatively high levels of the Topo I enzyme. Although the IGROV-Ptl (mutant p53 cell line) has relatively low levels of Topo I enzyme, the lack of a G1 checkpoint would have pushed the cells into G2. The G2 arrest may provide the cell with sufficient time for DNA repair, provided the damage is repairable. In addition to this G2 checkpoint, there may exist an additional S-phase checkpoint that may inhibit DNA replicon initiation, following formation of Topo I-drug complexes (4).

Caserini et al. (1) have shown the importance of a functional p53 in activating apoptosis following Topo I targeting. However, p53-mediated programmed cell death is probably only one of the many pathways through which Topo I inhibitors express their cell kill effect. It is well known that cells that do not express the wild-type p53 are still capable of undergoing apoptosis following lethal DNA damage. There may be other p53-independent signal perturbations that influence the apoptotic response. It is probably not essential to have a p53-mediated apoptotic pathway for the expression of Topo I inhibitor-mediated cytotoxicity. What other pathways may be involved in Topo I inhibitor-mediated apoptosis? There is some evidence to suggest that c-Jun-associated kinases and proteases may play a role. In myeloid leukemia U-937 cells, camptothecin has been shown to activate JNK1/stress-activated protein kinase, increase the c-Jun expression, and also activate interleukin-1β-converting enzyme/ced-3-like proteases. Interleukin-1β-converting enzyme/ced-3-like protease inhibitor, Z-Asp, blocked c-Jun-mediated apoptosis. Also, JNK1 antisense oligonucleotide diminished the synthesis of JNK1 protein and inhibited drug-induced apoptosis (5). Apoptotic machinery varies from tumor to tumor and from cell line to cell line; therefore, the above findings from the U937 myeloid leukemia cells may not apply to the ovarian tumors. In addition, intratumoral heterogeneity makes the issue more complex. The discrepancy between the in vitro and the in vivo systems may reflect, at least in part, the role played by stromal paracrine factors, modifying the apoptotic potential of an upstream signal. It would be very interesting to see whether such a mechanism exists in the ovarian tumor xenografts. Such stromal-mediated paracrine apoptotic influences have been described in other tumor systems (6).

In summary, Topo I inhibitors like topotecan induce apoptotic cell death via different pathways. Both p53-dependent and -independent apoptotic pathways have been documented. Equally, if not more significant, are the cell cycle perturbations associated with Topo I inhibition, which may determine the cytotoxic cell kill effect of Topo I poisons. Cyclins and cyclin-dependent kinases, in particular, p34cdc2/cyclin B, play a significant role in determining the ultimate fate of the cell after exposure to the camptothecin analogues. The effects of Topo I inhibitors on cell cycle progression and on the apoptotic pathways are important determinants of cytotoxicity. These variables should be taken into consideration before these novel agents are combined with existing anticancer drugs.

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1 The abbreviations used are: Topo I, topoisomerase I; JNK1, c-Jun NH2-terminal kinase.

References

6. Fujita, N., Kataoka, S., Naito, M., Heike, Y., Boku, N., Nakajima, M., and Tsuruo, T. Suppression of T-lymphoma cell apoptosis by Topo I inhibitors. These cellular events mediating chemosensitivity are common to a variety of DNA-damaging agents (2). Several lines of evidence suggest that the apoptotic response is a critical determinant of antitumor efficacy of cytotoxic drugs (2). The pattern of expression of multiple factors involved in regulation of apoptosis may be dependent on tumor type and biological background. In particular, concerning the activation of a p53-independent pathway of apoptosis by Topo I inhibitors, tumor type could critically influence the therapeutic response. Using tumor cells of epithelial origin (e.g., ovarian and lung carcinoma), inactivation of p53 could reduce sensitivity to DNA-damaging agents but not abolish cellular ability to trigger apoptosis. Indeed, apoptosis could be induced by relatively high concentrations of the cytotoxic agents. At effective drug concentrations, the extent of the apoptotic response may be even higher than that achieved by chemosensitive tumor cells with wild-type p53. Such an observation is consistent with the presence of a p53-independent mechanism of apoptosis. The expression of a functional wild-type p53 appears to lower the threshold at which drug-induced DNA damage triggers apoptosis. It is conceivable that p53-dependent and -independent pathways cooperate in determining cellular response to cytotoxic lesions (3).

The apoptotic machinery in leukemia cells could be different from that of solid tumors of epithelial origin that are responsive to DNA-damaging agents, as suggested by Bulusu (1). Indeed, there is evidence to suggest that, in some cell systems (e.g., HL60), p53 is not required for apoptosis activation by DNA-damaging cytotoxic agents (4). Thus, the induction of p53-independent apoptosis is cell-type-specific rather than drug-specific.

Bulusu (1) also emphasizes the involvement of cell cycle perturbations in determining the cytotoxic effects of Topo I inhibitors, which is also documented in our work (5). Such effects on chemosensitivity are very complex and are likely dependent on expression of regulatory genes (6) and on cell ability to recognize specific DNA lesions or cell injury. They may have important implications in the design of new effective combinations because drug-induced cell cycle perturbations may critically influence the interaction with other cytotoxic agents.

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