EDITORIAL

Vinorelbine: A Horse of a Different Color?

PROGRESS IN THE treatment of the most frequent solid tumors had been slow during the 1980s. This was due a pause in the development of drugs with new mechanisms of action, such as the taxanes and the topoisomerase I inhibitors. Despite the improvement of toxicity profile, analog development has failed to create other indications in solid tumors than those of the parent drugs, for example, epirubicin and carboplatin. We seem to be facing a different situation with the latest vinca analog, vinorelbine (3'-nor-anhydrovinblastine), which is a follow-up to drugs such as vincristine, vinblastine, and vin-desine. This agent is giving promising results and indeed seems to be an exception among the analog stories, with new indications for use of vinorelbine on the horizon.

This issue of the Journal of Clinical Oncology includes two reports on vinorelbine: one dealing mainly with the pharmacokinetics of the drug after oral administration and the second reporting the results of a phase II clinical trial of the combination of vinorelbine and doxorubicin as first-line chemotherapy in metastatic breast cancer.

This semisynthetic analog differs from the natural vinca alkaloids by the presence of an eight-member catharanthine ring instead of a nine-member ring. The target, however, remains cytosolic tubulin, a ubiquitous eukaryotic protein. Tubulin polymerizes and forms the microtubular system that plays an important role in nerve conduction, neurotransmission, and mitosis. Vinca alkaloids induce aggregation of tubulin into paracrystalline structures and promote a tubulin aggregation process modulated by the microtubule-associated proteins (MAPs). Vinorelbine seems to disorganize microtubules of the mitotic figure at a lower concentration than other vinca alkaloids and one at which it fails to affect the axonal microtubules. These observations led to the suggestion that vinorelbine might be less neurotoxic and more toxic to the cancer cell.

In the very first preclinical experiments, the drug showed major activity that was clearly superior to or equally effective as conventional vinca alkaloids. It was just not another analog.

Phase I evaluation of vinorelbine revealed the maximum-tolerated dose (MTD) to be a weekly dose of 35 mg/m², with neutropenia as the dose-limiting side effect. At the higher dose levels, mild peripheral neuropathy was also documented. The recommended dose level for phase II studies was 25 to 30 mg/m².

The report by Rowinsky et al represents a well-conducted pharmacokinetic study of vinorelbine in 17 heavily pretreated patients with different types of advanced solid tumors. In a randomized fashion, the patients initially received the drug either intravenously (IV) (30 mg/m²) or orally (100 mg/m²). Pharmacokinetics were also studied after the second oral drug administration to determine possible intrindividual variations in absorption. Weekly oral vinorelbine was continued thereafter at 100-mg/m² dose.

From the results, it is evident that vinorelbine has a large volume of distribution, a long terminal half-life, and a high clearance rate. These findings are in agreement with those reported by the French investigators, although Rowinsky et al found a shorter terminal half-life of 18 hours versus 44.7 hours observed by the French group. It also seemed that the bioavailability of vinorelbine after oral administration is low (27 ± 12%). A significant first-pass effect through the liver seems to be responsible for this low bioavailability of the oral formulation of the drug. A similar pharmacokinetic profile for oral vinorelbine has been reported recently by Zhou et al.

Although Rowinsky et al convincingly showed that the pharmacology of the oral route is essentially the same as that after IV administration, there is the question whether we should attempt to develop new oral anticancer drugs. The authors showed that even under optimal conditions, ie, after an 8-hour fasting period and 4 hours before the next meal, there was an intraindividual variation of some key pharmacokinetic parameters between the first and the second oral administration of vinorelbine. We have no idea how the absorption would be under ordinary daily conditions, but one should not be surprised to find even larger variations. Moreover, we believe that more information is needed on the present oral formulation before advocating its use. Problems with oral formulations have been well recognized in the past, and they have undoubtedly been a major reason to refrain from using this route of administration in drug development. Also, in studies such as this, detailed information on comedication, including morphine, other analgetics, and antiemetics, should be reported because of their affect on stomach emptying. In sum, the convenience of the oral route does not outweigh the inconvenience of the essential weekly blood-cell monitoring needed with the recommended weekly administration. Thus, for several reasons we favor the IV route, in particular when used in combination with other drugs and when one is not willing to compromise on dose-intensity. Alternatively, there is no clear benefit to be expected from the viewpoint of therapeutic efficacy of the drug. The only exception may be the use of single-agent treatment, applying a lower dose if phase II studies continue to show efficacy and if compromising the dose does not jeopardize the therapeutic efficacy greatly.

The second report on vinorelbine deals with its thera-
neutropenia. The authors noted that neloxabine, a drug derived from a vinca alkaloid, was shown to reduce the incidence of neutropenia in patients receiving doxorubicin and cyclophosphamide. The combination was also found to be well tolerated, with minimal toxicity and supportive care required. As a result, the addition of neloxabine to the existing regimen may improve outcomes for these patients.

In summary, neloxabine's potential role in the treatment of metastatic breast cancer seems promising. Further studies are needed to confirm its efficacy and safety in larger patient populations. The drug's mechanism of action offers a new approach for managing chemotherapy-induced neutropenia, potentially sparing patients from the adverse effects of conventional myelosuppressive agents.

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REFERENCES


