1. Ansfield FJ, Kallas GJ, Signson JP. Phase I–II studies of oral tegafur (ftorafur). *J Clin Oncol* 1983, 1, 107–110.
2. Creaven PJ. 5-fluorouracil and folinic acid: summary of clinical experience. In Rustum Y, McGuire J, Eds. *The Expanding Role of Folates and Fluoropyrimidines in Cancer Chemotherapy*. New York: Plenum Publishing Corp., 1989, 303–311.
3. Piedbois P, Buyse M, Rustum Y, *et al.* (Advanced Colorectal Cancer Meta-Analysis Project) Modulation of fluorouracil by leucovorin in patients with advanced colorectal cancer: evidence in terms of response rate. *J Clin Oncol* 1992, **10**, 896–903.
4. Hines JD, Zakem MH, Adelstein DJ, Rustum YM. Treatment of advanced stage colorectal adenocarcinoma with 5-fluorouracil and high dose leucovorin: a pilot study. *J Clin Oncol* 1988, **6**, 142–146.
5. McGuire BW, Sai LL, Leese PT, Stolestad ELR. Pharmacokinetics of leucovorin calcium after intravenous, intramuscular and oral administration. *Clin Pharmacy* 1988, 7, 52.
6. Zhang Z-G, Rustum YM. Effects of diastereoisomers of 5-formyltetrahydrofolate on cellular growth, sensitivity to 5-fluoro-2′-deoxyuridine and methylenetetrahydrofolate polyglutamate levels in HCT-8 cells. *Cancer Res* 1991, **51**, 3476–3481.
7. Rocci ML, Jr, Jusko WJ. LAGRAN program for area and moments in pharmacokinetic analysis. *Computer Programs Biomed* 1983, **16**, 2203–2216.
8. Zhang Z-G, Harstrick A, Rustum YM. Mechanisms of resistance to fluoropyrimidines. *Semin Oncol* 1992, **19**, 4–9.
9. Anttila MI, Sotaniemi EA, Kairaluoma MI, Mokka RE, Sundquist HT. Pharmacokinetics of ftorafur after intravenous and oral administration. *Cancer Chemother Pharmacol* 1983, **10**, 150–153.

Acknowledgements—This research was carried out as part of the US/Russia agreement in Cancer Research and Treatment. Supported in part by USPHS CA-21071.

Eur J Cancer, Vol. 29A, No. 12, p. 1794, 1993.
Printed in Great Britain
0959–8049/93 $6.00 + 0.00

Neurotoxicity After Chemotherapy With Vinorelbine

Federico Lonardi, Giovanni Pavanato, Vittorio Ferrari, Giorgio Bonciarelli, Antonio Jirillo and Mario Balli

VINORELBINE (VNB) is a semi-synthetic 5′nor-vinca alkaloid whose interesting antitumor activity seems coupled with mild toxicity. Leukopenia has been reported as the dose-limiting factor and neurotoxicity is characterised by constipation (40%) and paralytic ileus (1.5%).

We evaluated 27 patients with advanced solid cancers, most of them previously treated with radiotherapy and/or chemotherapy, who received VNB at the recommended weekly dose of 30 mg/m^2 (25 mg/m^2 in 4 patients with poor performance status and/or past heavy treatments), given in 20 min infusion without routine prophylactic antiemetics. The median number of administrations was 4 (range 1–11).

Toxicity was evaluable in 24 patients, as 3 were lost to follow-up after the first administration. According to WHO criteria, the worst haematological toxicity was grade III leukopenia in 4 previously chemo-treated patients. Peripheral neurotoxicity was negligible (grade I in 1 patient), but constipation emerged as the most prominent toxic effect in 7 patients (30%), two of them (9%) presented clinical signs of paralytic ileus. Particularly, constipation occurred at grade II–III after one administration in 3 previously untreated patients and with grade III in 2 patients who had received cisplatin-based chemotherapy; grade IV was observed after one administration at 25 mg/m^2 in 2 patients (breast and head and neck cancer), both treated earlier with heavy and prolonged chemotherapy. Symptoms recovered without sequelae after VNB discontinuation, but hospital admission and supportive care were needed in the latter 2 patients, whose paralytic ileus-related symptoms completely recovered after 5–7 days.

More toxic side-effects included nausea, grade II hair loss and moderate phlebitis on the site of injection.

The percentage of constipation cases we observed is consistent with other published data, but the grade was unexpected. All patients affected with constipation had neither particular neuropathological risk factors nor took narcotics prior or during chemotherapy, thus the onset of such an intense neurotoxicity remains unclear. Previous treatments with neurotoxic drugs seem a reasonable explanation but this does not apply to untreated patients. In summary our experience has confirmed VNB as an interesting drug with significant activity in advanced and pretreated patients (data not shown and to follow) but less manageable than expected. Myelotoxicity was not as severe in our case series as reported in the literature. We might conclude with a word of caution when VNB is planned in patients previously treated with potentially neurotoxic drugs.

Correspondence to F. Lonardi.
The authors are at the Divisione di Radioterapia-Oncologia, U.L.S.S.28-via Gianella 1, 37045 Legnago (Verona), Italy.
Received 24 Mar. 1993; accepted 19 Apr. 1993.

1. Krikorian A, Rahmani R, Bromet M, *et al.* Pharmacokinetics and metabolism of Navelbine. *Semin Oncol* 1989, **16**, 21–25.
2. Depierre A, Lemarie E, Dabouis G, *et al.* A phase II study of Navelbine® (vinorelbine) in the treatment of non small cell lung cancer. *Am J Clin Oncol* 1991, **14**, 115.
3. Krikorian A, Breillout F. Vinorelbine (Navelbine registered). A new semisynthetic vinca alkaloid. *Onkologie* 1991, **14**, 7–12.
4. Berthaud P, Le Chevalier T, Ruffie P, *et al.* Phase I/II study of vinorelbine (Navelbine) and high dose cisplatin (CDDP) in advanced non small cell lung cancer (NSCLC). *Proc Am Soc Clin Oncol* 1990, **9**, 918.
5. Delozier T, Delgado FM, Fumoleau P, *et al.* Phase II trial with navelbine (NVB) in advanced breast cancer (ABC). *Br Cancer Res Treat* 1990, **16**, 149.
6. Fumoleau P, Delgado FM, Delozier T, *et al.* Phase II trial with Navelbine (NVB) in advanced breast cancer (ABC): preliminary results. *Proc Am Soc Clin Oncol* 1990, **9**, 76.
7. Besenval M, Delgado M, Demarez JP, *et al.* Safety and tolerance of Navelbine® in phase I-II clinical studies. *Semin Oncol* 1989, **16**, 37–40.
8. Canobbio L, Boccardo F, Pastorino G, *et al.* Phase II study of Navelbine® in advanced breast cancer. *Semin Oncol* 1989, **16**, 33–36.
9. Demicheli R, Cavina R. Neurotossicità della Vinorelbina. Argomenti di Oncologia 1992, **13**, 153–157.