

Review

Vinorelbine – a clinical review

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Vinorelbine is a semi-synthetic vinca-alkaloid with a broad spectrum of anti-tumour activity. The vinca-alkaloids are categorized as spindle poisons, and their mechanism of action is to interfere with the polymerization of tubulin, a protein responsible for building the microtubule system which appears during cell division.

The original vinca-alkaloids were derived from the dried leaves of the Madagascan periwinkle (*vinca rosea*), but low yields of the active compound limited the range of compounds available for study (Johnson et al, 1960). Vinblastine and vincristine were the compounds initially derived from the plant and both consisted of a catharanthine moiety linked to a vindoline ring. Subsequently, vindesine, a desacetyl carboxyamid derivative of vinblastine, was developed.

Vinorelbine differs from the natural compounds by the presence of an eight rather than nine member catharanthine ring (Figure 1). It is formulated as a light yellow amorphous powder.

Pharmacology

Vinorelbine is a mitotic spindle poison that impairs chromosomal segregation during mitosis. It blocks cells at G2/M when present at concentrations close to IC₅₀: at higher concentrations there is production of polyploidy (Pierre Fabre Medicament, 1993). Microtubules (derived from polymers of tubulin) are the principal target of vinorelbine (Weisenberg, 1972). The chemical modification used to produce vinorelbine allows opening of the eight-member catharanthine ring with formation of covalent reversible bond with tubulin.

The relative contribution of different microtubule-associated proteins in the production of tubulin vary between neural tissue and proliferating cells and this has important implications. The capacity of vinorelbine to bind preferentially to mitotic rather than axonal microtubules has been demonstrated and might imply that neurotoxicity is less likely to be a problem than with the other vinca-alkaloids (Paintrand and Pignot, 1983; Binet et al, 1989a). Assessment of the minimum concentration of drug required to inhibit polymerization of the spindle, compared with damage to the axonal microtubule, shows a ratio of 20:1 (Meninger et al, 1989). An additional advantage over other vinca-alkaloids lies in the selective production of mitotic tubulin paracrystallization which may point to enhanced cytotoxic action (Binet et al, 1990).

Cytotoxicity has been demonstrated against a broad spectrum of human tumour cell lines (lung, breast, leukaemia, myeloma, colon, melanoma, CNS). The IC₅₀ lies between 1 and 50 nMol (Ashizawa et al, 1993) (see Table 1).

Received 23 June 1999

Revised 21 January 2000

Accepted 24 February 2000

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Molecular mechanisms of action

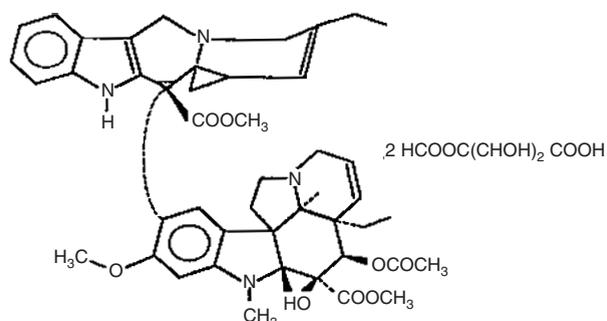
Like other anti-microtubule agents vinorelbine is known to be a promoter of apoptosis in cancer cells. The precise mechanisms by which this process occurs are complex and many details are yet to be elucidated. Disorganization of the microtubule structure has a number of effects, including the induction of tumour suppressor gene p53 and activation/inactivation of a number of protein kinases involved in key signalling pathways, including p21 WAF1/CIP1 and *Ras/Raf*, PKC/PKA (Wang et al, 1999a). These molecular changes result in phosphorylation and hence inactivation of the apoptosis inhibitor Bcl2 (Haldar et al, 1995). This in turn results in a decrease in the formation of hetero-dimers between Bcl2 and the pro-apoptotic gene BAX triggering the process of apoptosis in the cell (Wang et al, 1999b).

Toxicology

The dose-limiting toxicity of vinorelbine is leucopenia. Transient increase in SGOT and SGPT were noted in rats and dogs but not in monkeys. In intact tectal planes from mouse embryos, vinorelbine, vincristine and vinblastine were equipotent to induce a depolymerization of mitotic microtubules, but vinorelbine was less active on axonal microtubules than the other vinca-alkaloids (Binet et al, 1989b).

Table 1 Cytotoxicity of vinorelbine against human tumour cell lines

Origin	Number of lines studied	IC ₅₀ in nMol
Leukaemia	2	1.59–9.38
NSCLC	8	1.74–19.8
SCLC	1	4.82
Colon	5	2.25–49.3
Breast	2	19.10 (400 ^a)
CNS	2	2.06–4.60
Melanoma	5	1.6–24.00
Myeloma	6	0.00510–0.5

^a Line with MDR phenotype

Molecular weight: 1378 (base: 778 + 2 tartaric acid: 300)

Figure 1 Chemical structure of vinorelbine

Clinical pharmacology

The majority of data available for vinorelbine are based upon i.v. administration of the drug. Initial phase I studies of vinorelbine were performed in France, and the dose-limiting toxicity was leucopenia – at a dose of 27.5 mg m⁻² per week this was seen at grade 3 in 14% of cycles (Mathe and Reizenstein, 1985). In addition, some peripheral neuropathy was noted. Subsequent dose-finding studies, in which the dose was escalated from 30 mg m⁻² in 5 mg increments, found the MTD to be 45 mg m⁻² with the neutrophil nadir to be at day 8–10. Despite 50% of the patients sustaining grade 4 neutropenia or any grade 3 toxicity, none of the patients required hospitalization (Khayat et al, 1995). In clinical practice, many studies have demonstrated excellent dose-intensity with little significant toxicity using a schedule of 25–30 mg m⁻² i.v. Days 1 and 8 on a 21-day cycle.

Pharmacokinetics

The pharmacokinetic properties of vinorelbine have been well defined with the development of radioimmunoassay methods (Rahmani et al, 1984) and highly sensitive high-performance liquid chromatographic (HPLC) assays using fluorescence (Debal et al, 1992), ultraviolet (Jehl et al, 1990) or electrochemical detection (Van Belle et al, 1992). The pharmacokinetic properties of intravenously administered vinorelbine can be described by a three compartment model: after a dose of 30 mg m⁻² i.v. a high initial peak of 5 µmol rapidly decays to about 1 nmol at 2 h. Distribution in blood is rapid, with binding of 78% of the drug to platelets and a further 13.5% to plasma proteins with only 1.7% left as free drug in the first 2 h after administration. Subsequently, binding to plasma proteins is in the order of 70–80%. The drug diffuses freely into tissues showing a large volume of distribution and an elimination half-life of 40 h (Marquet et al, 1992).

Within 30 min of administration vinorelbine is highly concentrated in bile, excretory organs (spleen, liver and kidney), lung, muscle and heart in a range of experimental animals (Kobayashi et al, 1993). High levels of vinorelbine are found in both normal lung and tumour tissue and diffusion out of tumour tissue appears to be slow (Leveque et al, 1993). Brain and plasma levels are comparable in animal studies (Kobayashi et al, 1993). In pregnant rats drug is seen to cross the placenta and is detectable in the foetus (Van Belle et al, 1992).

There are some data available on the pharmacokinetics of the oral preparation of the drug which is currently in clinical trial. Vinorelbine has been evaluated as an oral preparation administered as a gelatin-filled capsule (Lucas et al, 1992) in women with advanced breast cancer (Spicer et al, 1994) and non-small cell lung cancer (Vokes et al, 1994). Initial studies have shown bioavailability for a soft liquid gelatin filled capsule to be 24% and for an unspecified formulation to be 40%; food did not appear to influence this (Van Cantfort et al, 1989). Within a dose range of 50–180 mg, peak plasma vinorelbine concentrations of 0.07–0.8 mg ml⁻¹ were seen at 1–2 h after administration of drug (Van Cartfort et al, 1989). The pharmacokinetic profile of orally administered vinorelbine is very similar to that seen with the intravenous route. The exception to this was an observed high clearance of 5.4 h⁻¹kg⁻¹ seen in nine patients treated in the preliminary studies, and it was proposed that this was due to first-pass hepatic metabolism (Cros et al, 1989).

Concentration–effect relationship

Data derived from testing against cell lines indicated that the IC₅₀ was between 1 and 50 nmol which is a concentration range readily

Table 2 Recommended dose modifications for vinorelbine in hepatic impairment

Bilirubin	Vinorelbine dose
≤2 mg dl ⁻¹	30 mg m ⁻²
2.1–3 mg dl ⁻¹	15 mg m ⁻²
>3 mg dl ⁻¹	7.5 mg m ⁻²

attained by standard dosing at 30 mg m⁻² which produces peak plasma levels of 1 µmol, with levels of 1 nmol present at 72 h (Leveque et al, 1992). Testing of the murine leukaemia model P-388 demonstrated a steep dose-response curve with response rates correlated to the total dose administered; these studies indicated that dosing at weekly intervals would be predicted to provide the most effective schedule (Cros et al, 1989).

Metabolism

The metabolism of vinorelbine is principally hepatic; only one metabolite, deacetylvinorelbine, has been identified, the activity of which is unknown (Jehl et al, 1991). Only 11% of the drug is excreted via the renal route, the majority being eliminated through faecal excretion (Bore et al, 1989). It is not known if the drug is excreted in breast milk.

As the liver provides the main route for metabolism of the drug it may follow that patients with hepatic impairment may show increased toxicity with standard dosing but there are no available data on this. Likewise the contribution of cytochrome P450 activity to vinorelbine metabolism has potential implications in patients receiving other drugs metabolized by this route (Leveque et al, 1992). There is no evidence that glucuronidation is involved in the metabolism of vinorelbine.

Mode of use

The drug is administered by intravenous infusion into the side-port of a running saline infusion over 6–10 min followed by a further flush through to the vein to minimize vessel irritation. Care should be taken to observe the infusion site as extravasation injuries may be severe (Rittenberg et al, 1995). In view of the potential of vinorelbine to produce painful phlebitis some centres administer it by central venous catheter only.

There are no data on patients with severe hepatic impairment, but it is recommended that the dose of vinorelbine be reduced in hepatic impairment according to the bilirubin (see Table 2). There is a lack of studies concerning renal insufficiency and administration of vinorelbine and the manufacturers advise caution before initiating therapy in this group of patients. There is no evidence that dose modifications are required in elderly patients with normal hepatic and renal function.

CLINICAL EFFICACY

Vinorelbine as single agent therapy in non-small cell lung cancer

So far over 15 trials with greater than 25 patients have been published using vinorelbine as a single agent in non-small cell lung cancer NSCLC and these are summarized in Table 3. The overall response rate in the published trials is 23.6%. In a recently

Table 3 Single agent vinorelbine in treatment of NSCLC

Author	Dose (mg m ⁻² per week)	Points	Overall response	Median survival (weeks)
Depierre et al, 1991	30	78	29.4%	33
Rinaldi et al, 1994	20	27	7%	–
Furuse et al, 1994	25	79	29.1%	40
Malzyner et al, 1991	30	36	33%	29.7
Crawford and O'Rourke, 1994	30	143	12%	30
Le Chevalier et al, 1994	30	206	14%	31
Gil Deza et al, 1996	30	73	42%	32.5
Furuse et al, 1994	25	103	31%	52.4
Veronesi et al, 1996	25–30	23	39.1%	38.7
Mattioli et al, 1997	30	15	20%	–
Gridelli et al, 1998	30	42	24%	35
Tononi et al, 1997	25	25	12%	43

Table 4 Navelbine/cisplatin in combination in NSCLC – Phase III trials

Author	Drug combination	Points	Response	Median survival (weeks)
Malzyner et al, 1991	N 30 mg m ⁻² weekly Cis 100 mg m ⁻² q28	39	36%	–
Depierre et al, 1991	N 30 mg m ⁻² weekly Cis 80 mg m ⁻² q21	116	48%	33
Le Chevalier et al, 1994	N 30 mg m ⁻² weekly Cis 120 mg m ⁻² q42	206	30%	40
Wozinak et al, 1998	N 25 mg m ⁻² weekly Cis 100 mg m ⁻² q28	206	26%	34
Gil Deza et al, 1996	N 30 mg m ⁻² weekly Cis 100 mg m ⁻² q28	83	42%	41
Gebbia et al, 1994	N 25 mg m ⁻² d1 + 8 Cis 100 mg ⁻² q28	50	38%	–

published phase III trial, 161 elderly patients were randomized to receive either vinorelbine or best supportive care; survival was significantly improved with vinorelbine (32% vs 14% respectively at 1 year, $P = 0.003$). In a quality of life analysis, functional scales were consistently better for vinorelbine; patients treated with vinorelbine scored better than controls for tumour-specific symptoms including pain and dyspnoea, but worse for toxicity, including constipation, nausea, hair-loss and neuropathy (The Elderly Lung Cancer Vinorelbine Italian Study, 1999). Single-agent vinorelbine seems a reasonable choice for administration in the elderly in whom polychemotherapy is not deemed possible.

Vinorelbine in combination chemotherapy in NSCLC

Vinorelbine has also been extensively tested in combination in NSCLC, most commonly with cisplatin. The published phase III trials of cisplatin-avelbine are shown in Table 4. A multi-centre European trial randomized patients to cisplatin (120 mg m⁻² day 1 and day 29 and then 6-weekly) plus vinorelbine (30 mg m⁻² weekly) or cisplatin and vindesine (3 mg m⁻² weekly for 6 weeks and then every 2 weeks) or vinorelbine alone. The cisplatin-vinorelbine combination had a superior response-rate of 30% compared to 19% for cisplatin-vindesine and 14% for vinorelbine alone; 1-year survival rates were 35%, 27% and 30% respectively (Le Chevalier et al, 1994). A pharmaco-economic analysis based on this study concluded that the most effective regimen of vinorelbine and cisplatin added substantial benefit to vinorelbine alone or another common regimen, vindesine/cisplatin, and a cost-effectiveness within accepted limits for medical interventions (Smith et al, 1995). A subsequent randomized phase III study from the SWOG group randomized 415 patients with advanced non-small cell lung cancer to receive either cisplatin 100 mg m⁻² q28 or

cisplatin 100 mg m⁻² and vinorelbine 25 mg m⁻² weekly. There was a statistically superior response-rate (12% vs 26%) and 1-year survival (20% vs 36%) in favour of the combination arm (Wozinak et al, 1998). Following this, studies have been performed comparing the cisplatin-avelbine combination with other combination regimens.

Vinorelbine has also been studied in combination with other drugs in non-small cell lung cancer. In a phase III study looking at the importance of sequencing, two-drug combinations cisplatin-vinorelbine performed well in advanced NSCLC compared to epirubicin-ifosfamide with response-rates of 47% and 21% respectively. Median overall survival was 13 months for the cisplatin-vinorelbine combination compared to 7 months for the epirubicin-ifosfamide combination ($P = 0.03$) (Colvcci et al, 1997).

Combined chemotherapy and radiotherapy is a common approach in the treatment of NSCLC. In a phase II study of 33 patients, cisplatin-vinorelbine was used as the induction regimen in patients with stage III-B disease prior to radical radiotherapy with an objective response of 48%, leading the authors to conclude that this is an effective regimen pre-radiotherapy (Felip et al, 1997).

The combination of carboplatin-vinorelbine would be an attractive alternative to cisplatin-avelbine, particularly in a more frail population, because of the lack of necessity for pre-hydration. However, one potential disadvantage of this regimen would be the possibility of severe myelosuppression given that this is the dose-limiting toxicity of both agents. Two-dose escalation studies have been performed looking at this combination. In the first, patients received carboplatin at an AUC of 7 and then increasing doses of vinorelbine up to 30 mg m⁻². Patients were able to tolerate the highest dose of vinorelbine but the majority required GCSF support (Crawford et al, 1994). In a subsequent study from Italy patients received a fixed dose of vinorelbine 25 mg m⁻² in conjunc-

Table 5 Single agent vinorelbine in treatment of metastatic breast cancer

Author	Dose (mg m ⁻²) per week	Points	Overall response	Median survival (weeks)
Canobbio et al, 1989	30	19	60%	–
Fumoleau et al, 1993	30	145	41%	78
Garcia-Conde et al, 1994	30	50	50%	65
Romero et al, 1994	30	44	41%	–
Weber et al, 1995	30	65	40%	67
Bruno et al, 1995	30	63	44%	50
Twelves et al, 1994	25	34	50%	41
Terenziani et al, 1996	30	27	59%	82

tion with carboplatin dose escalated from 300–400 mg m⁻². At top doses 19% of patients had grade III–IV neutropenia (Colleoni et al, 1996). The response-rate for this combination is encouraging, in one phase II study 77 patients with stage III and IV NSCLC received carboplatin 350 mg m⁻² D1 and navelbine 25 mg m⁻² D1 and D8 q28: response-rate was 31% with no grade IV toxicity observed (Santamaggio et al, 1996).

Paclitaxel is another relatively new drug that has attracted interest in the treatment of NSCLC. It has been combined with vinorelbine in a study of 18 patients with refractory metastatic NSCLC, and the overall response-rate was 27% with the most common side-effects being neutropenia and peripheral neuropathy (Chang et al, 1996). Several groups have investigated the combination of ifosfamide and vinorelbine. A phase I study performed by a US group found an overall response-rate of 40% with a 1-year survival rate of 48%. The regimen was highly tolerable with some patients continuing for 10 cycles (Masters et al, 1998). Cisplatin has also been added into this combination in a phase II study involving 76 untreated patients with advanced NSCLC with a response-rate of 52% and with neutropenia being the main toxicity necessitating the use of G-CSF in 27% of cases (Baldini et al, 1996). Similar response-rates were obtained using the triple combination of cisplatin-gemcitabine-navelbine in chemo-naive patients (Fiasci et al, 1997).

Vinorelbine as single agent therapy in metastatic breast cancer

Vinorelbine has shown a level of single-agent activity equivalent to that of many standard agents, including doxorubicin, epirubicin and mitoxantrone (1992), with a response-rate for first-line treatment of 40–60% (Fumoleau et al, 1993; Canobbio et al, 1989; Vogel et al, 1999); published trials are detailed in Table 5. The largest phase II trial on single-agent vinorelbine in metastatic breast cancer treated 145 women with 30 mg m⁻² weekly. The overall response-rate was 41%; patients with skin, lymph node and lung metastases seemed to do better than those with liver and bone metastases. Previous anthracycline as adjuvant chemotherapy did not appear to have any influence on response (Fumdeau et al, 1993). Clinical activity in the elderly shows similar response-rates to those seen in younger patients, with no need to dose-reduce (Canobbio et al, 1989). A recent study in which vinorelbine as single-agent treatment was used as first-line therapy for metastatic disease in patients over 60 showed a response of 38% with a median duration of response of 9 months, and low toxicity (Vogel et al, 1999). A phase II study of 183 patients comparing weekly vinorelbine to 3-weekly melphalan showed an improved time to progression (12 vs 8 months), an improved time to treatment

failure (12 vs 8 months) and improved overall survival (35.7% vs 21.7%) with vinorelbine (Jones et al, 1995). Economic assessments of anti-cancer treatments are becoming increasingly important to allow for targeting of resources. A recent cost-benefit analysis of single agents in anthracycline pre-treated patients with metastatic breast cancer compared vinorelbine, docetaxel and paclitaxel. The authors concluded that vinorelbine provided equivalent quality-adjusted disease-free survival with economic advantage over the taxanes (Leung et al, 1999).

Vinorelbine in combination therapy for metastatic breast cancer

Vinorelbine has principally been studied in combination with anthracyclines. Published trials are summarized in Table 6. The largest phase II study of vinorelbine/doxorubicin as first-line therapy for metastatic disease was performed in the UK with 117 patients receiving both drugs at a dose of 25 mg m⁻² on days 1 and 8 of a 21-day cycle; overall response-rate was 74% (Carmichael et al, 1997). In a randomized phase III study in 97 patients with hormonal resistant advanced breast cancer, the vinorelbine/doxorubicin combination achieved equivalent response-rates (34%) to the FAC (5-FU, adriamycin, cyclophosphamide) regimen (35%), and median duration of response was equivalent in the two groups (Blajman et al, 1996). Vinorelbine has also been studied in combination with epirubicin. In the largest published phase II series, 52 patients received vinorelbine and epirubicin both at a dose of 25 mg m⁻² weekly; the overall response rate was 77% with 75% of patients alive at 2 years (Nistico et al, 1997).

Mitoxantrone has also been tested in combination with vinorelbine. In a phase III trial patients were randomized to receive vinorelbine/mitoxantrone (MV) or a standard FAC/FEC regimen. The objective response-rates were similar (36% for MV vs 33% for FAC/FEC). For patients who had received prior adjuvant therapy those receiving the vinorelbine combination therapy had a significantly better response rate (33% vs 13%; $P = 0.025$), survival (20 vs 15 months; $P = 0.01$) and time to progression (8 vs 5 months; $P = 0.0007$) (Namer et al, 1997).

Vinorelbine has also been tested with other drugs in the treatment of advanced breast cancer. The combination of 5-fluorouracil and vinorelbine in 63 patients treated in a phase II study in France achieved a response rate of 64% with a median survival of 100 weeks (Dieras et al, 1996). Pre-clinical data suggesting synergy between vinorelbine and the taxanes have been confirmed in a phase II study of a combination of vinorelbine/paclitaxel showing a response-rate of 60% (Romerso et al, 1998). The combination of vinorelbine and paclitaxel appears particularly active. In a single-institution study from the USA, 32 patients with anthracycline pre-

Table 6 Navelbine/anthracycline combinations in metastatic breast cancer

Author	Drug combination	Points	Overall response	Median survival (weeks)
Spielmann et al, 1994	N 25 mg m ⁻² d1+8 Dox 50 mg m ⁻² q21	87	74%	118
Hochster et al, 1994	N 25 mg m ⁻² d1+8 Dox 50 mg m ⁻² q21	62	57%	–
Blajman et al, 1996	N 25 mg m ⁻² d1+8 Dox 50 mg m ⁻² q21	86	76%	82
Vorobiof et al, 1997	N 25 mg m ⁻² d1+8 Dox 50 mg m ⁻² q21	24	54%	–
Arca et al, 1998	N 25 mg m ⁻² d1+8 Dox 50 mg m ⁻² q21	70	68%	68
Carmichael et al, 1997	N 25 mg m ⁻² d1+8 Dox 25 mg m ⁻² d1+8	117	74%	–
Chadjaa et al, 1993	N 25 mg m ⁻² d1+8 Epi 60 mg m ⁻² q21	30	60%	36
Nistico et al, 1997	N 25 mg m ⁻² /week Epi 25 mg m ⁻² weekly	52	77%	43

treated metastatic breast cancer received infusional paclitaxel and weekly vinorelbine. Doses of both drugs were escalated according to liver function and all patients received scheduled GCSF support. Overall the response-rate was 50% with 22% of patients sustaining a complete response (Ellis et al, 1999).

Finally, consideration is now being given to the use of vinorelbine combinations in neoadjuvant and adjuvant chemotherapy. The French Oncology Group treated 104 patients with primary breast cancer with induction chemotherapy with navelbine/mitoxantrone. Overall response-rate was 45% with a 7% complete response. In total 64% patients were subsequently able to undergo conservative surgery (Adenis et al, 1996). Neutropaenia was the main toxicity with 83% of patients registering grade 3 neutropaenia. In summary, vinorelbine shows single-agent response-rates comparable to standard drugs in metastatic breast cancer and with low toxicity. In combination chemotherapy randomized trials containing the drug have shown equivalent or superior response-rates to standard combinations, again with less toxicity.

Other tumours

Vinorelbine has had some assessment in other malignancies. The combination of carboplatin-vinorelbine in small cell lung cancer has shown a response-rate of 74% (Gridelli et al, 1998) and is currently being investigated in the UK as a treatment for those patients with small cell lung cancer with a poor prognosis. In platinum-resistant ovarian carcinoma one study found single-agent activity of the drug to be 30% (Gershenson et al, 1998). Preliminary studies of vinorelbine in patients with cervical carcinoma recurring after radiotherapy found an overall response rate of 21% (Morris et al, 1998). It has been assessed in a range of B-cell malignancies as palliative treatment for extensively pre-treated patients. In patients with relapsed Hodgkin's disease 50% responded to vinorelbine with a median duration of remission of 6 months (Devizzi et al, 1994). In patients with relapsed multiple myeloma 61% of patients achieved stabilization of their disease with 16% achieving an objective response (Harousseau et al, 1997).

Toxicity

Vinorelbine is in general a well-tolerated cytotoxic agent but it does have some important toxicities.

Haematological

The main haematological toxicity seen with vinorelbine is neutropaenia and this is dose-limiting. Grade 3–4 neutropenia has been observed in 14–52% of patients treated with weekly intravenous vinorelbine; it is reversible, with a usual duration of 7–14 days, and is not cumulative, however dose adjustments have been required in up to 70% of patients (Cvittovic and Izzo, 1992). Thrombocytopenia is rare during therapy with vinorelbine.

Neurological

The vinca-alkaloids are recognized as causing neurological toxicity. Neurotoxic effects of vinorelbine include decreased deep-tendon reflexes, constipation, parasthesiae, myalgia, jaw pain and paralytic ileus. Peripheral neuropathy has been reported in up to 30% of patients receiving vinorelbine but this was severe, i.e. grade III or above, in only 1% (Navelbine Product Information). This is less than the other vinca-alkaloids; for example the incidence of peripheral neuropathy with vincristine is in the order of 57% (Cvittovic and Izzo, 1992).

Gastro intestinal effects

Severe nausea and vomiting are relatively infrequent with vinorelbine. Grade 3 or 4 toxicity has been reported in only 1–3% of patients (Cvittovic and Izzo, 1992; Dubos et al, 1991). Constipation and paralytic ileus have also been reported (Cvittovic and Izzo, 1992).

Venous access pain

Grade 3 or 4 cutaneous or venous reactions, e.g. pain on injection, venous pain and thrombophlebitis, have occurred in 5–10% of patients receiving vinorelbine (Besenval et al, 1991). This can to some extent be prevented by adequate flushing through of the vein with normal saline following injection of the drug. At the Royal Marsden Hospital these problems have been minimized by using a heat pad on the distal vein. In addition, patients receive a saline flush before and after the injection which is given over 6 min (Lisa Dougherty – CNS IV Services, personal communication).

Alopecia

This affects only 10% of patients treated with vinorelbine and is of minor severity. Very few patients experience total hair loss or require a wig.

Cardiovascular effects

Acute myocardial infarction has been reported following the administration of vinorelbine (Dubos et al, 1991).

CONCLUSION

Vinorelbine is an active new vinca-alkaloid with a different spectrum of activity from parent compounds. In particular it has high activity in breast cancer where it is one of the most active agents currently available, and it has useful activity in non-small cell lung cancer. Its relatively low incidence of side-effects makes it a useful new addition to the treatment of breast cancer and non-small cell lung cancer, and further combination studies are warranted.

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