introduction of 5FU after a cardiac failure episode has never been reported to lead to coronary spasms. This observation supports the hypothesis that a single pathophysiological mechanism could explain 5FU cardiotoxicity in terms of both ischaemic symptoms and cardiac failure. Our hypothesis is that 5FU might be responsible for coronary spasms, either proximal and localised with chest pain and ischaemic manifestations, or distal and global with cardiac failure, with or without chest pain. In this hypothesis, coronary spasms could be the common mechanism for all cardiac symptoms. More data are required to determine if prevention of coronary spasms could reduce the incidence of such manifestations.

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Severe 5-Fluorouracil Toxicity Possibly Secondary to Dihydropyrimidine Dehydrogenase Deficiency in a Breast Cancer Patient with Osteogenesis Imperfecta

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DIHYDROPYRIMIDINE DEHYDROGENASE (DPD) is the initial and rate-limiting enzyme in the uracil and thymine catabolism. DPD is also the principal enzyme involved in the degradation of the chemotherapeutic drug 5-fluorouracil, which acts by inhibiting thymidylate synthase. The clinical importance of DPD has recently been demonstrated with the identification of rare cases of a severe toxicity in patients with suspected or proven DPD deficiency [1, 2]. We report here a case of severe 5-FU toxicity related to DPD deficiency in a patient with concurrent congenital osteogenesis imperfecta (OI). A 45-year-old woman with phenotypic OI type I (multiple fractures since childhood, blue sclerae, hearing loss, normal stature) was treated with neoadjuvant chemotherapy for a stage II breast cancer. Familial history failed to find any previous case of tumour or OI. She received a first cycle of mitoxantrone 19 mg on day (d)1, cyclophosphamide 900 mg d1 and d8, 5-FU 900 mg d1, 3, 5, 8. By day 16, she was hospitalised with the following symptoms: fever, stupor, and WHO grade 4 diarrhoea and stomatitis. Biological tests demonstrated serious leucopenia (0.300 leucocytes/μl) and thrombopenia (31 000 platelets/μl). The patient defervesced on antibiotic therapy. She slowly improved and was discharged on day 30. She received a second course with reduced doses of mitoxantrone (14 mg d1) and cyclophosphamide (600 mg d1 and d8) and omission of 5-FU. The induced toxicity was mild with grade 2 neutropenia. Lymphocyte DPD activity, determined by a radioenzymatic assay using ^{14}C-5FU as substrate, was extremely low: 85 pmol/min per mg of protein, similar to other case reports of major toxicity with 5-FU. In fact, a close analysis of these few cases [1] revealed that, in these patients who developed severe 5-FU-related toxicity, lymphocyte DPD activity was always below 100 pmol/min/mg/protein. A population study of DPD performed on 185 unselected cancer patients [3] shows a median lymphocytic DPD activity value at 211 pmol/min/mg protein (range 65–559); 3% of this population exhibited a DPD activity below 100 pmol/min/mg protein. The incidence of OI

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is 1/10 000 newborn and the association of OI and malignancy has rarely been reported [4]. We were surprised to find another similar association of severe 5-FU toxicity related to DPD deficiency in a breast cancer patient with mild OI as reported by Lyss and associates [5]. The probability of a fortuitous association appears low. Specific major chromosomic alteration seems unlikely since no cytogenetic abnormality was found in this patient following high resolution karyotyping. OI type I is inherited in an autosomal dominant manner, although new mutations account for almost half of the affected individuals. With rare exceptions, OI is always the result of mutation in the genes *COL1A1* and *COL1A2* for the α1- and α2-chains of the major fibrillar collagen type I, located, respectively, on chromosomes 17q21-22 and 7q22. DPD deficiency has an autosomal recessive pattern of inheritance. The human DPD cDNA has recently been cloned and sequenced [6]. The gene was localised to the centromeric region of human chromosome 1 between 1p22 and 1q21. It is tempting to speculate that DPD activity may be abnormally regulated in OI patients.

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Vinorelbine/5-FU Combination in Metastatic Breast Cancer Chemotherapy. A Retrospective Study of 63 Cases

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VINORELBINE IS a semisynthetic vinca-alkaloid analogue, which has proved to be of interest in first-line palliative chemotherapy in patients with metastatic breast cancer, with a response rate of 41% [1]. During a phase II trial in first-line palliative breast cancer chemotherapy, it achieved a 62–72% objective response rate when combined to a 5-day continuous perfusion of 5-FU [2, 3].

Between July 1991 and November 1993, this treatment was given to 63 patients with metastatic breast cancer in our Institute. Mean age of patients was 48 years (range 29–69 years). All the patients had received at least one anthracycline-based chemotherapy regimen either during the treatment of the primary tumour or as a palliative treatment (Table 1). Among the 50 patients having undergone chemotherapy for the treatment of the primary tumour, when vinorelbine/5-FU was administered as a first-line palliative treatment, 21 patients had an early relapse (≤12 months). The median number of drugs previously received was six (range 3–11), and all the patients had received one vinka-alkaloid and/or bolus 5-FU. Most of these patients had a poor prognosis: 39% had liver metastases and 66% had at least two metastatic sites.

This chemotherapy combined vinorelbine (30 mg/m^2/day, i.v., days 1 and 6) and 5-FU (750 mg/m^2/day × 5) in continuous perfusion, every 22 days. WHO criteria were used to assess response to treatment and toxic effects [4]. The chemotherapy was continued until there was evidence of disease progression or unacceptable signs of toxicity. Patients underwent 1–25 chemotherapy cycles (median: 3). Theoretical doses of vinorelbine/5-FU were reduced immediately by 25% in 31 patients (49%) owing to their precarious performance status and/or hepatic disturbances.

One complete and five partial responses were observed giving an objective response rate of 9.5% (95% CI: 2–18%), with an average response duration of 5 months (range 3–15 months).

Disease was stabilised in 8 patients (12.7%), and time to disease progression ranged from 4 to 17 months.

The main side-effects were haematological and digestive. 13 patients experienced grade 3 or 4 leucopenia, 4 had grade 3 or 4 thrombopenia, and 6 had grade 3 anaemia. Stomatitis

Table 1. Prior treatments

Neo-adjuvant and/or adjuvant chemotherapy for the treatment of primary tumour	Palliative chemotherapy regimens delivered before vinorelbine/5-FU	Totals
Neo-adjuvant chemotherapy only* (n = 27)	none: 18 one: 4 two: 5	
Neo-adjuvant and adjuvant chemotherapy* (n = 9)	none: 5 two: 2 three: 2	none = 25 one = 7
Adjuvant chemotherapy only† (n = 14)	none: 2 one: 1 two: 8 three: 3	two = 23 three = 7 four = 1
No neo-adjuvant and/or adjuvant chemotherapy (n = 13)	one: 2 two: 8 three: 2 four: 1	

*Neo-adjuvant or adjuvant treatment: EVM (epirubicin, vincristine, methotrexate) × 3 cycles + MTV (mitomycin C, thiotepa, vindesine) × 3 cycles. †CMF IV: 9 cycles, or EVM × 3 cycles + MTV × 3 cycles.

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