Other examples of cytoregulated responses are seen in patients with carcinoid tumours. Treatment with interferon reduces subjective symptoms and improves the quality of life in the majority of patients although only about 10% responded with a reduction in tumour size. Furthermore, half of the treated patients experienced a more than 50% reduction in the tumour marker 5-hydroxy indole acetic acid [2, 4]. Another example is seen in patients with myelodysplastic syndrome treated with granulocyte-macrophage stimulating factor which may cause a reduction in the rate of infections compared to non-treated patients [5]. Two studies of myelodysplastic syndromes have indicated that interferon therapy reduces the rates of serious infections, independently of the haematological response [6, 7]. It has also been suggested that treatment with interferon or interleukin-2 offer a certain survival advantage among patients with renal cell carcinoma from the categories "no change" or "stable disease" [8, 9]. Additive hormonal therapy in patients with breast cancer is theoretically known to induce cell differentiation of the clonogenic cells, which are in the transition phase [10]. The end results might be a more differentiated cell population which loses its proliferation potential. Many of the tumour cells will consequently remain resting and tumour response in terms of "no change" can remain for months or years.

In these examples reliance on tumour shrinkage alone, which is the norm in phase II clinical trials, would have implied a high risk of rejecting a potentially beneficial therapy as inefficient. Response criteria for modern cancer therapy must therefore deal with all the pathophysiological manifestations of the neoplasia, the homoeostatis and the total psychosomatic wellbeing.

In summary, we suggest that the "homoeostatic concept" is included as an additional qualitative measure of the response to cancer therapy. The concept illustrates the positive effect biological response modifiers have on the disease manifestation and life quality of patients with stable neoplastic disease.

1. Mandelli F, Avvisati G, Amadori S, *et al.* Maintenance treatment with recombinant interferon alfa-2b in patients with multiple myeloma responding to conventional induction chemotherapy. *N Engl J Med* 1990, **322**, 1430–1434.
2. Öberg K, Eriksson B. Medical treatment of neuroendocrine gut and pancreatic tumors. *Acta Oncol* 1989, **28**, 425–431.
3. Bergström M, Muhr C, Lundberg PO, *et al.* Modulation of tumor metabolism using hormonally acting drugs in patients with meningeoma. *J Endocrinol Invest* 1989, **12**(Suppl. 2), OC 1.
4. Hanssen LE, Schrumpf E, Kolbenstvedt AN, *et al.* Treatment of malignant metastatic midgut carcinoid tumors with recombinant human alfa-2b interferon with or without prior hepatic artery embolization. *Scand J Gastroenterol* 1989, **24**, 787–795.
5. Schuster MW, Larson RA, Thompson JA, Coiffier B, Bennett JM, Israel RJ. Granulocyte-macrophage colony-stimulating factor (GM-CSF) for myelodysplastic syndrome (MDS): results of a multicenter randomized controlled trial. *Blood* 1990, **76**(Suppl. 1), 1263.
6. Galvani D, Nethersell A, Bottomly J. Treatment of myelodysplasia with alfa-interferon. *Leukemia* 1987, **1**, 786–787.
7. Gisslinger H, Chott A, Linkesch W, Fritz E, Ludwig H. Long-term alfa-interferon therapy in myelodysplastic syndromes. *Leukemia* 1990, **4**, 91–94.
8. Trump DL, Elson PJ, Borden EC, *et al.* High dose lymphoblastoid interferon in advanced renal cell carcinoma: an eastern cooperative oncology group study. *Cancer Treat Rep* 1987, **71**, 165–169.
9. Wang JCL, Walle A, Novogrodsky A, *et al.* A phase II clinical trial of adoptive immunotherapy for advanced renal cell carcinoma using mitogen-activated autologous leukocytes and continuous infusion interleukin-2. *J Clin Oncol* 1989, **7**, 1885–1891.
10. Poulsen HS. *In vitro* observations in relation to response. In: Stoll BA, ed. *Endocrine Management of Cancer 1: Biological Bases*. Basel, Krager, 1988, 72–83.

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Severe Mucositis after Chemotherapy with Vinorelbine, 5-fluorouracil, Leucovorin and Cisplatin

Isabelle Monnet, Patrick Chariot, Nacer Azli, Pierre Ruffié, Sabine Voisin, Jean-Claude Saltiel, Hubert de Cremoux and Esteban Cvitkovic

WE HAVE developed a chemotherapy regimen for non-small cell lung cancer with vinorelbine (Navelbine®), 5-fluorouracil (5-FU), leucovorin and cisplatin. Vinorelbine is 5′-nor-anhydrovinblastine, a vinca alkaloid derived from vinblastine by partial synthesis [1]. As with other spindle poisons, vinorelbine inhibits the assembly of microtubules and induces an arrest of cells in the metaphase of mitosis [2]. We report a high frequency of severe mucositis.

18 patients were treated with vinorelbine 20 mg/m^2 on days 1 and 8, 5-FU by continuous infusion 600 mg/m^2 daily on days 1–4, leucovorin 150 mg/m^2 four times daily on days 1–4, and cisplatin 100 mg/m^2 day 1 repeated once every 3 weeks. We noted grade 3 or 4 mucositis (WHO classification) in 11 cycles out of 25 (44%) and grade 3 or 4 neutropenia in 10 cycles out of 22 (45%). 3 patients died from sepsis during an episode of severe mucositis and neutropenia (grade 4). The study was stopped because of unacceptable toxicity.

The treatment-related complications were particularly severe and frequent compared with those observed in our previous trial [3], which used vindesine by continuous infusion 0.8 mg/m^2 daily on days 1–4 instead of vinorelbine: 50 patients had been treated and grade 3 or 4 mucositis had been observed in 18 cycles out of 131 (14%), grade 3 or 4 neutropenia in 53 cycles out of 131 (40%), and 1 patient died from sepsis during a neutropenic episode. Regimens including 5-FU are known to induce mucosal and haematological toxicities. Administration of 5-FU by continuous infusion can reduce both haematological and mucosal toxicities and improve the antitumour efficacy [4]. The addition of leucovorin could also improve the antitumour efficacy of 5-FU [5], but has been associated with a higher rate of toxic mucositis [6]. Vinorelbine has proved its efficacy as a single agent in non-small cell lung cancer [7]; neutropenia and peripheral neuropathy were the most frequent toxic effects in four phase II studies, and no mucosal toxicity was noted [8, 9]. However, a high rate of mucositis was observed when vinorelbine was associated with 5-FU by continuous infusion in metastatic breast carcinoma [10].

We suggest that vinorelbine significantly potentiates 5-FU-induced mucosal toxicity, especially when 5-FU is associated with leucovorin. Prudence is needed in the design of a regimen associating these drugs.

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1. Mangeney P, Andriamialisoa RZ, Lallemand JY, Langlois N, Langlois Y, Potier P. 5'-Nor anhydrovinblastine, prototype of a new class of vinblastine derivatives. *Tetrahedron* 1979, **35**, 2175–2179.
2. Binet S, Fellous A, Lataste H, Krikorian A, Couzinier, Meininger V. *In situ* analysis of the action of Navelbine® on various types of microtubules using immunofluorescence. *Semin Oncol* 1989, **16** (Suppl. 4), 5–8.
3. Monnet I, Azli N, Voisin S, *et al.* 5-fluorouracil/leucovorin/vindesine/cisplatin in non-small cell lung cancer: a phase II study. *Proc Am Soc Clin Oncol* 1991, **10**, A 879.
4. Lokich JJ, Ahlgren JD, Gullo JJ, Philips JA, Fryer JG. A prospective randomized comparison of continuous infusion fluorouracil with a conventional bolus schedule in metastatic colorectal carcinoma: a Mid-Atlantic Oncology Program Study. *J Clin Oncol* 1989, 7, 425–432.
5. Arbuck SG. Overview of clinical trials using 5-fluorouracil and leucovorin for the treatment of colorectal cancer. *Cancer* 1989, **63**, 1036–1044.
6. O'Connell MJ. A phase III trial of 5-fluorouracil and leucovorin in the treatment of advanced colorectal cancer. A Mayo Clinic/North Central Cancer Treatment Group Study. *Cancer* 1989, **63**, 1026–1030.
7. Depierre A, Lemarie E, Dabouis G, Garnier G, Jacoulet P, Dalphin JC. Efficacy of Navelbine® (NVB) in non small cell lung cancer (NSCLC). *Semin Oncol* 1989, **16** (Suppl. 4), 26–29.
8. Besenval M, Delgado M, Demarez JP, Krikorian A. Safety and tolerance of Navelbine in phase I-II clinical studies. *Semin Oncol* 1989, **16** (Suppl. 4), 37–40.
9. Canobbio L, Boccardo F, Guarneri D, *et al.* Phase II study of navelbine in advanced renal cell carcinoma. *Eur J Cancer* 1991, **27**, 804–805.
10. Dieras V, Varette C, Louvet C, Espié M, Colin P, Marty M. Association Navelbine® -5-fluoro-uracile dans le traitement de première intention d'adénocarcinomes mammaires métastatiques. In: Solal-Celigny P, ed. *Navelbine: Actualités et Perspectives*. London, John Libbey, 1990, 225–231.

Corrections

Cancer in the European Community and its member states. — In this article by Dr O. Møller Jensen *et al.* (Vol. 26, 1167–1256), the number of new cases of cancer in the Summary and on p. 1171 should have read 1222 120 and not 1186 000. The same applies to the accompanying editorial by C.S. Muir and P. Boyle (p. 1112).

Intraperitoneal chemotherapy for malignant peritoneal mesothelioma. — In this article by Dr L.Th. Vlasveld *et al.* (Vol. 27, 732–734), the fifth sentence of the final paragraph of the discussion should have begun: "Furthermore, the data presented in Tables 1 and 2..."

Comparison of the sulforhodamine B protein and tetrazolium (MTT) assays for *in vitro* chemosensitivity testing. — In this article by Dr Y.P. Keepers *et al.* (Vol. 27, 897–900), the units for IC_{50} in Table 1 should have been μmol/l.

Double-blind randomised trial of the antiemetic efficacy and safety of ondansetron and metoclopramide in advanced breast cancer patients treated with epirubicin and cyclophosphamide. — In this article by Dr N.W. Marschner *et al.* (Vol. 27, 1137–1140) the references should have read as follows:

1. Canellos GP, De Vita VT, Gold GL, *et al.* Combination chemotherapy for advanced breast cancer: respose and effect on survival. *Ann Intern Med* 1976, **84**, 389–392.
2. Hortobagyi GN, Bodey GP, Budzar AU, *et al.* Evaluation of high-dose versus standard FAC chemotherapy for advanced breast cancer in protected environment units: A prospective randomised study. *J Clin Oncol* 1987, **5**, 354–364.
3. Wilcox PM, Fetting JH, Nettlesheim KM, Abeloff MD. Anticipatory vomiting in women receiving cyclophosphamide, methotrexate and 5-flourouracil (CMF) adjuvant chemotherapy for breast carcinoma. *Cancer Treat Rep* 1982, **66**, 1601–1604.
4. Gralla RJ, Tyson LB, Kris MG, Clark RA. The management of chemotherapy induced nausea and vomiting. *Med Clin North Am* 1987, **71**, 289–301.
5. Roila F, Tonato M, Basurto C, Minotti V, Ballatori E, Del Favero A. Double-blind controlled trial of the anti-emetic efficacy and toxicity of methylprednisolone (MP), metoclopramide (MTC) and domperidone (DMP) in breast cancer patients treated with CMF. *Eur J Cancer Clin Oncol* 1987, **23**, 615–617.
6. Cunningham D, Evans C, Gazet J-C, *et al.* Comparison of anti-emetic efficacy of domperidone, metoclopramide and dexamethasone in patients receiving outpatient chemotherapy regimens. *Br Med J* 1987, **295**, 250.
7. Cunningham D, Pople A, Ford HT, *et al.* Prevention of emesis in patients receiving cyto antagonists. *Lancet* 1987, 1461–1463.
8. Cox R, Newman CE, Leyland MJ. Metoclopramide in the reduction of nausea and vomiting associated with combined chemotherapy. *Cancer Chemother Pharmacol* 1982, **8**, 133–135.
9. Gralla RJ. Metoclopramide. A review of anti-emetic trials. *Drugs* 1983, **25** (Suppl.1), 63–73.
10. Grunberg SM, Akerley WL, Krailo MD, *et al.* Comparison of metoclopramide and metoclopramide plus dexamethasone for complete protection from cisplatin-induced emesis. *Cancer Invest* 1986, **4**, 379–385.
11. Gunning SJ, Hagan RM, Tyers MB. Cisplatin induces biochemical and histological changes in the small intestine of the ferret. *Br J Pharmacol* 1987, **90**, 135P.
12. Cubeddu L, Hoffmann I, Fuenmajor M, Finn AL. Ondansetron, an antagonist of serotonin 5-HT-3 receptors prevents vomiting induced by cisplatinum- and cyclophosphamide containing chemotherapy regimens. *Proc Am Soc Clin Oncol* 1990, Abstr 1281.
13. Andrews PLR, Hawthorn J, Sanger GJ. The effect of abdominal visceral nerve lesions and a novel 5-HT-3 receptor antagonist on cytotoxic and radiation induced emesis in the ferret. *J Physiol* 1986, **382**, 47P.
14. Tyres MB, Bunce KT, Humphrey PP. Pharmacological and anti-emetic properties of ondansetron. *Eur J Cancer Clin Oncol* 1989, 25 (Suppl. 1), 15–19.
15. Einhorn LH, Nagy C, Werner K, Finn AL. Ondansetron: A new anti-emetic for patients receiving cisplatin chemotherapy. *J Clin Oncol* 1990, **8**, 731–735.
16. Bonneterre J, Chevallier B, Metz R, *et al.* A randomized double-blind comparison of ondansetron and metoclopramide in the prophylaxis of emesis induced by cyclophosphamide, flourouracil and doxorubicin or epirubicin chemotherapy. *J Clin Oncol* 1990, **8**, 1063–1069.
17. Kaasa S, Kvaloy SL, Dicato MA, Ries F, Huys JV, Royer E, Carruthers and the International Emesis Group. A comparison of ondansetron with metoclopramide in the prophylaxis of chemotherapy-induced nausea and vomiting: a randomized, double-blind study. *Eur J Cancer* 1990, **26**, 311–314.
18. Priestman TJ. Clinical studies with ondansetron in the control of radiation induced emesis. *Eur J Cancer Clin Oncol* 1989, **25** (Suppl. 1), 29–33.
19. Marschner NW, Nagel GA, Bruntsch U, *et al.* Oral GR38072F as anti-emetic prophylaxis in patients receiving cyclophosphamide containing chemotherapy regimens. *Cancer Chemother Pharmacol* 1989, **23** (Suppl), Abstr. 266(P).
20. Mantel N. Chi-square tests with one degree of freedom: extensions of the Mantel Haenszel procedure. *J Am Stat Association* 1963, 58, 690–700.
21. Pendergrass K, Hainsworth J, Harvey W, Kasimis B, Finn A. Ondansetron (OND): more effective than metoclopramide (MCP) in the prevention of cisplatin (DDP)-induced nausea (N) and vomiting (V). *Proc ASCO* 1990, Abstr 1234.

Report on consensus meeting of the EORTC Melanoma Group on educational needs for primary and secondary prevention of melanoma in Europe. — In this article by Dr R.M. Mackie *et al.* (Vol. 27, 1317–1323), Dr Kölmel's address was wrongly ascribed as Göttingen, The Netherlands. The correct country is F.R.G.