European Journal of Cancer Vol. 30A, No. 3, p. 420, 1994.

0959-8049/94 $6.00 + 0.00

Treatment of Patients with Metastatic Melanoma with a One Day Regimen of Dacarbazine, Vincristine, Bleomycin and Lomustine plus Interferon-α

M. Vuoristo, P. Gröhn, E. Kumpulainen and M. Korpela

PREVIOUS STUDIES on interferon-α-2b (IFN-α2b) combined with chemotherapy have reported response rates of 23–53% in metastatic melanoma [1, 2].

We carried out a phase II study of metastatic melanoma with four-drug chemotherapy plus recombinant IFN-α in 1990–1991. The treatment consisted of dacarbazine 700 mg/m^2 intravenously (i.v.), vincristine 2 mg i.v., bleomycin 30 mg i.v. and lomustine 80 mg orally (DOBC) every 28 days plus IFN-α2b 3×10^6 U (Intron-A®, Schering-Plough) subcutaneously three times weekly. 9 patients (5 males and 4 females, aged 28–67 years, median 58 years) with measurable metastatic melanoma were enrolled for the study. The metastatic sites were the lung (5 patients), the lymph nodes (3 patients), the liver (3 patients) and the skin (2 patients). 5 patients had multiple metastatic sites. The response and adverse effects were evaluated according to the WHO criteria [3].

All patients were evaluable for toxicity and 8 patients for response. The response rate was low: only 1 patient achieved partial response in lung metastases lasting for 5 months and another had stable disease lasting for 3 months. The overall survival of the responding patient was 12 months. The median survival of all patients was 5 months (range 2 weeks–32+ months). The treatment was moderately toxic. The flu-like syndrome attributable to IFN was controlled by non-steroidal anti-inflammatory drugs. The most common adverse reactions of chemotherapy were cytopenia, gastrointestinal symptoms and alopecia (Table 1). There was one treatment-related death caused by haematotoxicity. It was concluded that the present regimen offers no benefit for patients with melanoma.

Table 1. Toxicity of the treatment (DOBC plus IFN-α2b)

	WHO grade	
Adverse event	1–2	3–4
Haematological	3	3
Gastrointestinal	7	1
Alopecia	4	0
Neurological	2	0
Stomatitis	1	0

Values expressed are numbers of patients.

Correspondence to M. Vuoristo at the Department of Oncology, University of Tampere and Tampere University Hospital, 36280 Pikonlinna, Finland.
P. Gröhn is at the Deaconess Hospital in Helsinki, Alppikatu 2, 00530 Helsinki; E. Kumpulainen is at the Department of Radiotherapy and Oncology, Kuopio University Hospital, 70210 Kuopio; and M. Korpela is at the Department of Radiotherapy and Oncology, Oulu University Central Hospital, 90220 Oulu, Finland.
Revised 8 July 1993; accepted 13 Sept. 1993.

1. Falkson CI, Falkson G, Falkson HC. Improved results with the addition of interferon alfa 2b to dacarbazine in the treatment of patients with metastatic malignant melanoma. *J Clin Oncol* 1991, **9**, 1403–1408.
2. Gröhn P, Kumpulainen E, Nuortio L, *et al.* A phase II study of metastatic melanoma treated with a combination of interferon alpha-2b, dacarbazine and nimustine. *Eur J Cancer* 1992, **28A**, 441–443.
3. Miller AB, Hoosgstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.

Acknowledgements—We wish to thank the Cancer Society of Pirkanmaa for supporting this study.

European Journal of Cancer Vol. 30A, No. 3, pp. 420–421, 1994.

0959-8049/94 $6.00 + 0.00

Bioavailability of Oral Etoposide in Gastric Cancer

B.G. Taal, J.H. Beijnen, F.G.M. Teller, W.W. ten Bokkel Huinink, R. Dubbelman and H. Boot

IN THEIR recent report, Pinkerton *et al.* [1] described a 48% bioavailability of etoposide in children, and they advised a twice daily administration based on the short half-life of the drug. In adults, recent pharmocokinetic studies showed similar data with wide variations, and found better resorption at the lower dosages: 76% ± 22 bioavailability at an oral dose of 100 mg, and 48% ± 18 with a 400 mg dose [2]. As knowledge of the specific mechanism of this topoisomerase II inhibitor is increasing, there is a growing interest in the oral application [3]. The oral route seems to be simple and safe, as well as effective. Experience in small cell lung cancer suggests that long-term oral administration of etoposide is superior to short-term intravenous administration, which is reflected in much improved response rates [2]. In developing drug schedules with protracted oral etoposide, especially in combination with other cytostatic drugs, the dose-dependent variation in bioavailability is very important. We would like to report on another possible problem in bioavailability.

Recently, we performed a phase II trial in gastric cancer using the ELF regimen (etoposide, high dose leucovorin and 5-fluorouracil), as described previously by Preusser [5]. To improve results, we modified the regimen using oral doses of etoposide. However, in patients with gastric carcinoma the stomach is often either pathologically or surgically removed, and one might assume that this would interfere with the bioavailability of orally administered agents. Therefore, a pharmacoki-

Correspondence to B.G. Taal.
B.G. Taal, F.G.M. Teller and H. Boot are at the Department of Gastroenterology; W.W. ten Bokkel Huinink and R. Dubbelman are at the Department of Medical Oncology; and J.H. Beijnen is at the Department of Pharmacology, Netherlands Cancer Institute/Antoni van Leeuwenhoekhuis, Plesmanlaan 121, 1066 CX Amsterdam, the Netherlands.
Received 17 Aug. 1993; accepted 6 Sep. 1993.

netic study was performed in 8 consecutive patients of our phase II trial of the modified ELF regimen. Included were 8 males, median age 56 years (range 39–66), four gastric and four cardia carcinoma, two following resection (partial resection type Bilroth II, proximal gastric resection), two local recurrence after resection, and four with the primary tumour *in situ*. Sites of metastatic disease were the liver in 4, lymph nodes in 5 and malignant peritonitis in 1 patient.

In the pharmacokinetic study, etoposide was given on day 1 at a dose of 50 mg intravenously in 10 min, on day 3 one capsule of 50 mg orally, and from day 4 to day 15 50 mg twice a day. In following courses, etoposide was administered at a fixed dose of 2x50 mg days 1–15. In addition, leucovorin (300 mg/m^2) and 5-fluorouracil (500 mg/m^2) were given intravenously at the same dosage as in the original ELF regimen [5]. The oral bioavailability, area under the curve (AUC) orally/AUC intravenously, was 58% ± 16. This finding is similar to the 57% reported by D'Incalci [6] in 1982, and not greatly different from the dose-dependent findings in the recent report of Hande[2].

In conclusion, bioavailability of orally administered etoposide did not seem to be grossly impaired in patients with a pathologically or partially resected stomach.

1. Pinkerton CR, Dick G, Aherne GW. 24-hour plasma etoposide profile after oral and intravenous administration in children. *Eur J Cancer* 1993, **29A**, 1479–1481.
2. Hande KR, Krozely MG, Greco FA, Hainsworth JD, Johnson DH. Bioavailability of low-dose oral etoposide. *J Clin Oncol* 1993, **11**, 374–377.
3. Slevin MI, Joel SP. Prolonged oral etoposide in small cell lung cancer. *Ann Oncol* 1993, **4**, 529–532.
4. Comis RL. Oral etoposide in oncology: an evolving role. *Ann Oncol* 1992, **14** (suppl.), A3.
5. Wilke H, Preuser P, Fink U, *et al.* High dose folinic acid/etoposide/5-fluorouracil in advanced gastric cancer—a phase II study in elderly patients or patients with cardiac risk. *Invest New Drugs* 1990, **8**, 65–70.
6. D'Incalci M, Farina P, Sessa C, *et al.* Pharmacokinetics of VP16-213 given by different administration methods. *Cancer Chemother Pharmacol* 1982, **7**, 141–145.

European Journal of Cancer Vol. 30A, No. 3, pp. 421–422, 1994.

0959–8049/94 $6.00 + 0.00

Why Don't We Use a "Cavalieri"?

J. K. D. Bentzen

IN PHASE II and III trials with chemotherapy, it is common practice to use the terms CR (complete response), PR (partial response), NC (no change) and PD (progressive disease) in evaluation of treatment response. The WHO definitions of these terms are based on a two-dimensional assessment of tumour size [1]; the largest diameter of the tumour is measured, and multiplied by the diameter perpendicular to it. PD is defined as a 25% increase in size as defined above, and PR is defined as at least a 50% reduction in tumour size. Assuming that tumours are spheroid in shape, and that they grow or shrink equally in all three dimensions, the actual changes in tumour volume corresponding to the WHO criteria are 40% for PD and 65% for PR. In other words, a treatment is not stopped until the tumour has grown by 40%, and a response is not classified as 'PR' until the tumour is reduced to 35% of its initial size. Any changes between these are classified as 'NC'. This way of measuring tumour size is rather inadequate but, nevertheless, we still use the WHO criteria for evaluation, in spite of having access to three dimensional information such as computed tomography (CT) or magnetic resonance (MR) scans.

I would like to suggest a very simple and more exact method of determining tumour volumes from CT scans. The method is borrowed from the relatively new scientific field of stereology, but the principle was originally described by the sixteenth century (1598–1647) Italian mathematician Cavalieri [2]. According to the principle of Cavalieri the volume, V, of an object can be determined by cutting it into parallel slices separated by a known distance, t, summing up the areas of the cross sections and multiplying by t. Then, $V = t \times \sigma$ area is a close approximation to the true volume.

The only condition is that the first section must be placed at random in the object. This principle is ideal when you have a tumour visualised on CT slides. The precise distance between the slides is well known (usually 1.0 cm) and the tumour area from each slide can very easily be estimated. A sheet of transparent film with marked, regularly arranged reference points, each point a known area [a(p)] (corrected for the magnification of the scans), is superimposed randomly over each of the scans containing the tumour. On each scan, the number of points within the tumour are counted (σp). The size of the tumour (v) can then be estimated from the following simple equation: $V(\text{tumour}) = t \times a(p) \times \sigma p$. For example, if the t = 1.0cm, a(p) =0.25 cm^2 and σp = 77 points then $V(\text{tumour}) = 1.0\ \text{cm} \times 0.25\ \text{cm}^2 \times 77 = 19.25\ \text{cm}^3$.

The precision of the method is very much dependent on the irregularity of the object measured. For tumours that tend to be more or less spheroid in shape, approximately 75 points should be counted in no less than five slides to give an unbiased estimate of the true volume, with a precision better than 5% [1–6].

If the tumour is less than 5 cm, perpendicular to the scanning plane, a distance between slices less than 1.0 cm must be used in order to have at least five scans containing tumour, but this should not cause any problems. Once familiar with the method, counting the necessary points takes minutes. With this level of precision, waiting until the tumour volume has grown by 40% before stopping the treatment of a patient with an ineffective drug will no longer be necessary since 10% will probably be sufficient. Similarly, waiting until the tumour volume is reduced to 35% before classifying a PR will not be necessary, and many of the NCs encountered in chemotherapy trials can be categorised as either PRs or PDs.

Furthermore, if this method becomes generally accepted and a specified precision for reporting results is agreed upon, then comparison of results from different centres will be more meaningful. The method is easy, precise and unbiased and I strongly recommend it be implemented.

Correspondence to J.K.D. Bentzen at the Fasanvaenget 107, 2980 Kokkedal, Denmark.
Received 23 Aug. 1993; accepted 6 Sep. 1993.