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Treatment of Good-risk Disseminated Non-seminomatous Germ Cell Tumours: the Less Bleomycin, the More Cisplatin?

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THE SEARCH for continued refinement in the treatment of germ cell non-seminomatous tumour patients has been emphasised [1]. Given the high cure rate achieved through the introduction of cisplatin based chemotherapy, reduction of toxicity is a suitable endpoint in patients with good risk disease. The three-drug regimen BEP (bleomycin, etoposide, cisplatin) is the standard treatment for these patients. Because of the associated pulmonary and vascular toxicity, limiting the use of bleomycin has been the objective of several trials.

So far, two randomised studies compared the efficacy of cisplatin plus etoposide (EP) with or without bleomycin and led to apparently conflicting results [2, 3]. At Indiana University, 178 patients were treated with three cycles of cisplatin (20 mg/m^2) plus etoposide (100 mg/m^2) both given on days 1–5 every 3 weeks, with or without bleomycin (30 IU weekly × 9). The study was suspended early because interim analysis demonstrated a significant ($P = 0.03$) increase in the number of adverse events on EP arm [2]. The second trial was conducted by the EORTC and compared four cycles of cisplatin (20 mg/m^2, days 1–5) plus etoposide (120 mg/m^2, days 1, 3, 5) every 3 weeks, with or without bleomycin (30 IU weekly × 12). In a preliminary analysis, the efficacy of both regimens is not significantly different[3].

Cumulative doses and dose intensities of the drugs delivered in these two trials are detailed in Table 1. The observed divergent results cannot be related to etoposide: the cumulative doses are roughly the same, and the dose intensity is weaker in the EORTC study. Therefore we suggest that the cumulative dose of cisplatin (400 vs. 300 mg/m^2) is the relevant point which may explain the better efficacy of the EP arm in the EORTC trial. The 92% disease-free survival achieved by three cycles of BEP is similar to that observed in patients receiving four cycles of that regimen [4]. Consequently, deleting bleomycin in patients receiving four cycles of etoposide plus cisplatin or limiting the cumulative dose of bleomycin to three cycles of BEP should be two equivalent alternatives.

Table 1. Comparison of cumulative doses and dose intensities of drugs in two randomised trials in good risk non-seminomatous germ cell tumours

			Cisplatin		Etoposide		Bleomycin		
Institution	Protocol		DI	CD	DI	CD	DI	CD	Adverse events
Indiana University	3	BEP	33	300	166	1500	30	270	13/83
	3	EP	33	300	166	1500	0	0	26/83
									$P = 0.03$
EORTC	4	BEP	33	400	120	1440	30	360	14/79
	4	EP	33	400	120	1440	0	0	17/75
									NS

DI = Dose intensities in mg/m^2 per week except for bleomycin (IU per week), CD = cumulative doses in mg/m^2 except for bleomycin (IU), NS = not significant, BEP = bleomycin, etoposide, cisplatin, EP = etoposide, cisplatin.

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Homoeostatic Response Criteria for Cancer Therapy

Erik Hippe, Viggo Jønsson, Hans von der Maase, Jens Christian Mathiesen and Hans Skovgaard Poulsen

THE USE of biological response modifiers such as interferons, interleukins, growth factors and hormones can prolong the duration of remission and survival [1] and improve the neoplastic cell function [2]. In contrast to the cytostatics, these agents stimulate a spectrum of metabolic processes in tumour cells and normal cells. Thus, the traditional assessment of cancer therapy based on tumour reduction may be insufficient in the evaluation of the efficacy of biological response modifiers. The response achieved with these modifiers may be a controlled tumour cell function rather than a tumour reduction. Such a "cytoregulated response" has been shown by Bergström *et al.* who reported a reduction in tumour cell metabolism in meningeoma after treatment with interferon [3] without a simultaneous reduction in tumour size as demonstrated by computed tomography (CT).

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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.

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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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