Fatigue in cancer patients receiving chemotherapy: an analysis of published studies

In their review article, Iop et al. [1] carefully evaluated the usually overlooked problem of fatigue in cancer patients receiving chemotherapy, and they should be congratulated on their work. However, we would like to stress the point that cancer-related fatigue also occurs in patients after the time of therapy, and without any connection to the kind of chemotherapy they have received. Fatigue occurring during chemotherapy is predictable, unlike that which develops in patients who are not receiving chemotherapy, which can last years after chemotherapy. Usually this cancer-related fatigue is a non-specific, multidimensional construct characterized by debilitating lassitude unrestored by rest, decreased capacity in maintaining performance, generalized weakness defined as the anticipatory sensation of difficulty in starting a new activity, mental fatigue defined as the presence of impaired mental concentration, loss of memory and emotional lability. Sleep disorders are also frequently reported. Joly et al. [2] reported a statistically significant difference in chronic fatigue in long-term survivors of Hodgkin’s disease in comparison with healthy controls. The fatigue levels in these patients remain high even years after treatment. In addition, Andrykowski et al. [3] and Broeckel et al. [4] found higher levels of fatigue, more weakness and less vitality following treatment for breast cancer compared with a matched group of women with no history of cancer. This fatigue syndrome seems to be similar to the one observed in patients (without cancer) who are affected by chronic fatigue syndrome according to the CDC definition [5]. However, the definition of chronic fatigue syndrome is based on exclusion criteria, and cancer is one of the diseases that must be excluded prior to this diagnosis. In conclusion, during a follow-up visit medical oncologists should be aware of the fact that cancer-related fatigue could have developed in their patients and should therefore take care that this syndrome is not ignored.

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Randomized phase II study evaluating oxaliplatin alone, oxaliplatin combined with infusional 5-fluorouracil and infusional 5-fluorouracil alone in advanced pancreatic carcinoma patients

Advanced pancreatic carcinoma carries a poor prognosis, with a median survival ~3–6 months. In a randomized phase II study of patients with advanced pancreatic carcinoma, Ducreux and colleagues evaluated oxaliplatin 130 mg/m² alone, oxaliplatin with 5-fluorouracil (5-FU) (1000 mg/m² days 1–4) and 5-FU alone [1]. Combination chemotherapy gave the best results, with a response rate of 10%, median time to progression of 4.2 months and median survival of 9 months. Nevertheless, this study is questionable in several aspects. The first point is the choice of the single-agent arms, which led to short survivals (2.4 and 3.4 months with 5-FU and oxaliplatin, respectively), confirming its inefficacy. The current study started in November 1997, despite the fact that after the publication of Burris et al. [2] in June 1997, gemcitabine rapidly became the standard care. Moreover, gemcitabine administered at fixed dose rate seems to be even more efficacious. Although combinations of 5-FU and cisplatin have frequently been used in patients with good general status in France, 5-FU alone has not been administered for many years. Despite an inevitable selection of relatively favourable cases, several recent studies have demonstrated that 5-FU alone gives no responses and does not prolong survival [2, 3].
Moreover, both continuous infusion and modulation by leucovorin have failed to increase the efficacy of 5-FU [4, 5]. It gives no advantage in combination with gemcitabine [6]. Above all, continuous infusion is extremely restrictive for patients with a very short life expectancy. Given synergies with many drugs, it is also true that oxaliplatin gives higher response rates in combination, typically in tumors with higher chemosensitivity such as colorectal carcinoma or ovarian carcinomas. Nevertheless, a phase II study of the combination of gemcitabine and oxaliplatin showed modest results, with a median time to progression of 4.5 months, suggesting no evidence of superiority over gemcitabine alone [7]. Although oxaliplatin is usually included in the FOLFOX regimen, Ducreux and colleagues [1] have created a new variant, increasing the confusion. A tremendous number of phase II studies exploring doublets with various combinations of old and new drugs including taxanes, irinotecan, platinum compounds or fluoropyrimidines have been published since the end of the 1990s, showing, at best, marginal improvements. The evolution of this proliferation of phase II studies to phase III studies would take decades. Given the poor prognosis and low probability of obtaining significant improvements with the current cytotoxic drugs, quality of life should remain one of the primary objectives for pancreatic carcinoma. In this regard, the oral route as well as regimens compatible with home chemotherapy should be preferred. A certain number of factors that are predictive of response to chemotherapy, such as CA 19-9, serum albumin, total bilirubin, C-reactive protein or performance status, might be applied. Since the vast majority of the patients do not benefit from current costly regimens, while on the other hand there are good responders with prolonged survival and an increasing variety of drugs, studies should be orientated towards molecular predictive factors of response to a given drug.

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Response to the letter

The authors thank Dr Alliot for his thoughtful letter, and agree with most of his considerations, discussion and well thought-out approach to the possibility of finding molecular predictive factors for specific drugs or regimens. Nonetheless, some misconceptions and/or misunderstandings need to be clarified with respect to the timing and rationale for the published study [1], so that his comments can be considered in the correct context.

Most of the authors of our paper are indeed firm advocates of the fixed rate gemcitabine infusion, which was first prospectively assessed in a comparative trial reported in abstract form in 1999 by Tempero et al. [2] as a more efficient (more active, less toxic) way to administer this agent. This led one of the participants to design the optimal GEMOX (gemcitabine–oxaliplatin) (E.C.) combination later adopted by the GERCOR group in its studies on this disease [3].

Gemcitabine was not approved for the treatment of pancreatic cancer in France until April 1998, given its minimal benefit over what we consider suboptimal (bolus) administration of 5-fluorouracil (5-FU). On the other hand, our choice of