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Editorial comment

Non-randomised phase II trials of drug combinations: often meaningless, sometimes misleading. Are there alternative strategies?

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The main objective of clinical research in oncology is to investigate new treatment approaches for cancer patients and document potential therapeutic benefit in a way convincing enough to change clinical practice. With extremely rare exceptions, this requires one or several positive randomised phase III trials, adequately powered and addressing clinical end-points relevant to the patient, eventually combined in a meta-analysis. Those studies including hundreds or sometimes thousands of patients are the ultimate step of a multiple consecutive trials strategy that minimises the total number of patients put at risk of receiving a suboptimal (either not effective, or potentially harmful) treatment. Results of each study guide the decision to move on to the next one.

Development of a new agent starts with phase I trials, to document a safe dose range, and phase II trials, to document the level of biological activity against the targeted tumour type. For this purpose, shrinkage of cancer lesions is considered as a reasonable indicator of antitumour activity, and objective response criteria have been established to measure 'tumour shrinkage' in a standard way. In the guidelines recently published by the Response Evaluation Criteria In Solid Tumors (RECIST) working party [1], Therasse and colleagues underline that response rate is an appropriate tool to screen new anticancer agents, but cannot be sufficient, if taken alone, to document therapeutic benefit.

As soon as a trial is conducted with the aim to document a possible therapeutic 'benefit' in the studied patient population, and therefore includes an element of comparison, a major concern is to avoid patients' selection bias that can lead to erroneous results. For this reason, phase III clinical trials are always randomised [2]. Phase II studies of drugs combinations (and also of multimodality approaches) are generally conducted in patients for whom a (standard) therapy is available, that can hopefully be improved. Underlining fundamental differences in their objectives, the European Organization for Research and Treatment of Cancer (EORTC) has proposed to call them 'phase II feasibility studies', as opposed to 'single agent phase II studies', and recommends randomisation, using the standard treatment as the control arm [3].

In the present issue of the *European Journal of Cancer*, Laack and colleagues [4] report the results of a phase II trial investigating a combination of gemcitabine, vinorelbine and cisplatin in advanced non-small cell cancer. With a response rate between 27 and 64% (95% Confidence Intervals (CIs)), they conclude that their results are in range of those reported by others for combinations with the same drugs (varying from 33 to 65%) and nearly identical to the response rates reported for other triple drug combinations. They have subsequently initiated a phase III trial comparing their three-drug regimen with a two-drug regimen.

Based on a similar design, Taïeb and colleagues [5] have included 42 patients with oesophageal cancer in an uncontrolled phase II trial of an investigational regimen of hydroxyurea, leucovorin, 5-fluorouracil (5-FU) and cisplatin (HLFP). With a response rate between 42 and 72% (95% CIs), they concluded that the HLFP regimen is as promising as other combinations, and should be compared with the classical 5-FU/cisplatin regimen in a phase III trial. In a prognostic factor analysis, they demonstrate an important influence of the type of metastases on the response rate; this suggests the possibility of

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a large selection bias in all of the trials conducted in this population.

How much did the results of these two trials contribute to the decision to move ahead? A more effective strategy would have included randomisation against standard therapy in the phase II trial, with the possibility of further extension into a phase III trial. This would have saved time and money, without increasing the number of patients at risk of receiving a suboptimal treatment.

Wagener and colleagues [6] have randomised 36 patients with metastatic pancreatic cancer between two new combinations (5-FU and cisplatin versus 5-FU, cisplatin and interferon), but without a standard arm with 5-FU alone. The limited number of observed responses, in both arms, has led them to conclude that these regimens could not be recommended (for further testing). One can, however, wonder how much impact patient selection had on these poor results; randomisation versus 5-FU alone would have helped in answering this question.

More importantly, results of uncontrolled phase II trials may be largely misleading and, therefore, dangerous.

The development of 'second and third generation' regimens to replace the established cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) standard chemotherapy for intermediate and high grade non-Hodgkin's lymphoma in the early 1980s illustrates the danger of this approach. From 1983, the results of non-randomised phase II trials investigating five new dose intensive combinations were published. Sample sizes ranged from 61 to 134 patients, and complete response rates ranging from 61 to 82% [7–11] were reported, contrasting with the 50% complete response rate historically reported for CHOP. Those results generated not only an abundant literature, but also a large number of subsequent studies without any CHOP control arm, aiming at 'confirming', 'improving' or 'comparing' the activity of these new regimens. However, the five major trials that did include randomisation versus the CHOP (or a CHOP-like) regimen, published between 1992 and 1996, unanimously demonstrated that none of the new combinations improved response rate, progression-free survival or overall survival, and that all resulted in increased toxicity and toxic deaths rates [12–16]. Miller concluded that "much of the controversy regarding treatment for diffuse large cell lymphoma resulted from inappropriate comparisons of results of new studies to historic CHOP trials without regard for major differences in patients selection" [17]. During nearly 10 years (1983–1992), large numbers of patients have been treated with high dose regimens, inside or outside trials. These patients would have been spared unnecessarily toxic treatment if the initial phase II trials had included randomisation versus CHOP. Should this have happened in the World Wide Web era, patient refusal to participate in randomised phase III trials would even have endangered their completion.

The more recent example of high dose therapies with autologous bone marrow transplant in breast cancer shows that we learn slowly from past experience. The highly significant benefit suggested by initial phase II trials with historical controls, both for advanced [18,19] and high-risk early disease [20,21] resulted in the treatment of more than 41 000 women in the 1990s with high-dose chemotherapy regimens despite the lack of evidence of efficacy [22]. So far, this has cost massive amounts of money, and resulted in many patients being exposed to toxicity and some mortality. Two fraudulent trials have been conducted, aiming at proving the biased belief [23,24]. Because of the consequent difficulty to recruit patients into randomised trials, the final answer is still unknown, as recently demonstrated by Antman [25] in a review of the available data. Up-front randomisation would probably have avoided this situation that damaged the credibility of the oncology community.

Today, the recommendations made by the EORTC in 1997 are more relevant than ever. Randomised phase II trials do not have any intent of formal comparison and are insufficiently powered for statistical tests (unless they are further extended as phase III trials). However, they offer a protection against possible selection bias. With their internal controls, they avoid the temptation of historical comparisons, not only for treating physicians, but also for patients who are generally unaware of the limited validity of results of uncontrolled studies. Statisticians advocate to 'randomise your first patient' whenever a standard therapeutic option is available. This principle largely applies to cancer research, even outside of phase III trials, with the exception of single agent phase I and II trials that are generally conducted in patients beyond any therapeutic options.

One can also question the choice of 'response to treatment' to guide further development of a combination therapy. It is unlikely that a combination of active drugs would result in an inactive treatment, and the level of activity, measured by the objective response rate alone, is not always a reliable surrogate for therapeutic benefit. Progression-free rates could be interesting alternative end-points to decide to start or carry-on a phase III trial investigating survival benefit.

However, do we need any safeguard to start a phase III trial when the optimal doses of the combination have already been defined in phase I trials? Will a preliminary phase II trial spare patients from being put at risk of receiving a suboptimal treatment? Appropriate interim analyses and stopping rules foreseen in the design of the phase III trial can easily replace the phase II step. Monitoring of interim results by an Independent Data Monitoring Committee would guarantee that the trial remains worthwhile and ethical until its completion.

This strategy relies largely on the quality of the phase I trials, which should provide enough evidence of the

combination safety. However, if the confidence in their results is limited, or if some doubts arise in their generalisation outside of centres specialised in new drug development, a close monitoring plan can be implemented for the first randomised cohort of patients. Randomisation here will also protect against the eventual selection bias that can largely influence the side-effects.

Apparent drawbacks of up-front randomisation include the complexity, cost and duration of the trial before the first decision point: the number of required patients is generally doubled. A loss indeed, if the development of the combination is stopped at this point. However, otherwise, this should be considered as an investment that will ultimately decrease the complexity, cost and duration of the global project.

If the phase III trial(s) is (are) ultimately completed, the up-front randomisation option is definitely the cheapest: not only in terms of costs proportional to the total number of patients (this approach requires less patients in total), but also in terms of the trial initiation costs, linked to the preparation, approval and implementation of a new clinical trial, that have dramatically increased in recent years.

Good Clinical Practice Guidelines, as well as national and international regulations, presently impose the same quality standards to all types of trials, and randomisation adds little complexity to the design, preparation, performance and monitoring of a clinical trial. However, writing only one protocol and obtaining single ethics approval would be beneficial. This approach is certainly the fastest one, and it ensures that the investigators and their team do not lose their impetus or expertise in a break between trials.

Non-randomised phase II trials with drug combinations will rarely provide crucial or decisive information for the development of the treatment strategy. They can probably be skipped, if phase III trials are adequately planned and monitored, or alternatively replaced by randomised phase II feasibility trials that can be extended into phase III studies. Objective response rate is not an optimal end-point for the decision rule. The up-front randomisation strategy decreases the total number of patients needed to bring a new drug combination into clinical practice, the number of patients submitted to a potentially suboptimal therapy and the total cost and duration of the treatment development.

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