Pergamon

European Journal of Cancer, Vol. 33, Suppl. 2, pp. S8–S10, 1997

Printed in Great Britain
0959–8049/97 $17.00+0.00

PII: S0959-8049(96)00447-9

Anticancer Drug Evaluation: Continuing Progress from Existing Methodology

W. ten Bokkel Huinink

The Netherlands Cancer Institute, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands

Current methods of anticancer drug evaluation are responsible for past successes, such as the development of cisplatin and other well-established agents. Phase II trials based on meticulously measured response rates provide an excellent tool for the identification of promising compounds whose exact place in the clinic may be further clarified in subsequent, larger studies. On the same basis, the many inactive compounds may be screened out after testing them in only a handful of patients. After a period of lull, this established methodology is once more yielding important breakthroughs. © **1997 Elsevier Science Ltd. All rights reserved.**

Key words: anticancer drug screening, phase II studies, response rates
Eur J Cancer, Vol. 33, Suppl. 2, pp. S8–S10, 1997

INTRODUCTION

THE GOAL of the development of new anticancer agents is to cure cancer. To this end, current methods of assessing anticancer agents have not failed. Indeed, they have, to their credit, been responsible for the many successes of anticancer treatment to date, among which the early work on improving the therapeutic index of cisplatin, by Cvitkovic and others, is an elegant example [1]. These pioneering studies facilitated the effective management of cisplatin toxicity in the clinic, and the subsequent successes of cisplatin, particularly in testicular cancer, must be attributed to this research. With 5-year and 10-year survivals approaching 100% in testicular cancer treated with hemicastration and cisplatin-based chemotherapy in the case of relapse (relapse following hemicastration occurs in around 25% of patients), testicular cancer is rightly regarded today as an eminently curable disease.

PHASES OF ANTICANCER DRUG DEVELOPMENT

Anticancer drug development follows a well-established schedule.

- Phase I studies assess the toxicity of a test agent, defining its maximum tolerated dose (MTD) and dose-limiting toxicity (DLT), and determining the dose to be used in subsequent studies.
- Next, phase II studies measure the antitumour activity and define toxicity further. Only if useful antitumour activity is documented in phase II does the agent progress to phase III.
- Phase III studies are the comparative trials that assess the effectiveness of the agent in relation to standard comparators.

Thus, phase II trials act essentially as a screening process for the elimination of useless compounds. It must be emphasised that most phase II studies yield completely negative results. It is, therefore, important to limit the number of patients who are exposed to a new, and probably inactive, agent to a minimum.

RESPONSE RATE AS THE KEY ENDPOINT IN PHASE II

In Europe, the large-scale phase II testing of new anticancer drugs is well co-ordinated through the combined work of the EORTC Early Clinical Trials Group and the Clinical Screening Group, and the New Drug Development Office [2]. The primary endpoint used in such testing is response rate. Standard WHO and EORTC response rate criteria are used to define response [3, 4]. If the response rates documented in phase II are 'promising' (> 20%), the drug enters phase III trials, in which survival or cost–benefit endpoints become relevant.

A major factor determining the use of response rate as the key endpoint is the need to screen our inactive compounds as quickly as possible in as few patients as possible. The working hypothesis in European anticancer drug evaluation is that a drug with a response rate of less than 20% has no useful antitumour activity. Using this hypothesis, if no response is seen in any of the first 14 patients, the chance that the drug will be falsely rejected (i.e. the rejection error) is under 5%. On this basis, therefore, if no responses are seen, a useless compound may be withdrawn from study after treating only 14 patients.

In a recent collaboration between The Netherlands Cancer Institute and a group in France, the screening out of a worthless compound was conducted successfully using even smaller numbers of patients. In phase II testing of vintriptol, a potential new vinca alkaloid to add to the wide range of these agents available already, it was decided that the new agent would only be worthy of further evaluation if a response rate of at least 30% could be documented. On this basis, working to a rejection error of less than 5%, only 9 patients needed to be treated without response before the trial was stopped. The

collaborative groups were, therefore, able to screen the (worthless) compound in four separate tumour types (breast cancer, colorectal cancer, lung cancer and melanoma) in a total of only 36 patients. No antitumour activity was documented [5].

DEFINITION OF RESPONSE RATE

In drug development trials, response must be accurately assessed. Both the WHO and EORTC provide clear guidelines on how to define target lesions, on setting consistent response criteria and in grading toxicity. Despite recent improvements in consistency of reporting results in anticancer clinical trials, a range of different terms and phrases relating to response still appear in the literature. The initiative of the EORTC to address both the methodology and classification of response is contributing to this improvement. In the author's view, researchers should document responses only, and refrain from referring to 'no change' or 'minimal response'.

For a patient to be documented as having a response, all measurable lesions should decrease by at least 50% in cross-sectional area, and this improvement must last for more than 3 months. (Current regulations stipulate that the improvement must be maintained only for more than 4 weeks, but a repeated computed tomography scan at 4-week intervals is not possible in all hospitals, so 3 months is a more practical time period.) No measurable lesions should progress, and each lesion must be weighed separately.

ROLE OF SURVIVAL AND OTHER ENDPOINTS

The disease-free survival of patients is, of course, the ultimate aim of all cancer treatment. In the longer-term, evaluation of a given agent's value, therefore (i.e. in phase III and subsequently), survival and other endpoints, such as quality of life, become significant. Indeed, survival is the primary endpoint of phase III studies. With a survival endpoint, however, a larger patient sample is necessary and, particularly when a Kaplan–Meier curve is plotted rather than actuarial survival, the trial may take years to yield a result.

This is one of the main reasons why survival is impractical as a primary endpoint in phase II trials. If the drug being tested achieved lasting stabilisation of patients' disease in phase II, it may be argued that researchers using survival as their endpoint could wait endlessly—and needlessly—for another patient to die. In fact, I would argue that if survival had been the endpoint for the early work on, for example, cisplatin, etoposide, doxorubicin, cyclophosphamide, methotrexate, 5-fluorouracil or mercaptopurine, we might still be waiting for these agents today.

Another problem with using survival as an endpoint in phase II studies is the lack of a valid group for the comparison of results. The comparison of survival in responding versus non-responding patients is questionable as these groups may have very different prognostic factors, such as the rate of tumour growth or patient performance status. This has been highlighted previously [6].

Thus, the importance of prognostic factors in determining survival must not be underestimated (Table 1). Knowledge of the exact population demographics is essential for the accurate analysis of all survival data. Patients in phase II usually have a high tumour burden, are heavily pretreated and have poor performance status. Almost inevitably, their long-term survival is unlikely.

Even in phase III trials and subsequently, prognostic factors remain important. The valuable role played by cisplatin in ovarian cancer, for example, only became clear when progression-free survival (rather than survival as a whole) was determined [7]. The reason for this is that cisplatin has often been used after failure of a non-cisplatin regimen (i.e. in patients with an inherently poor prognosis).

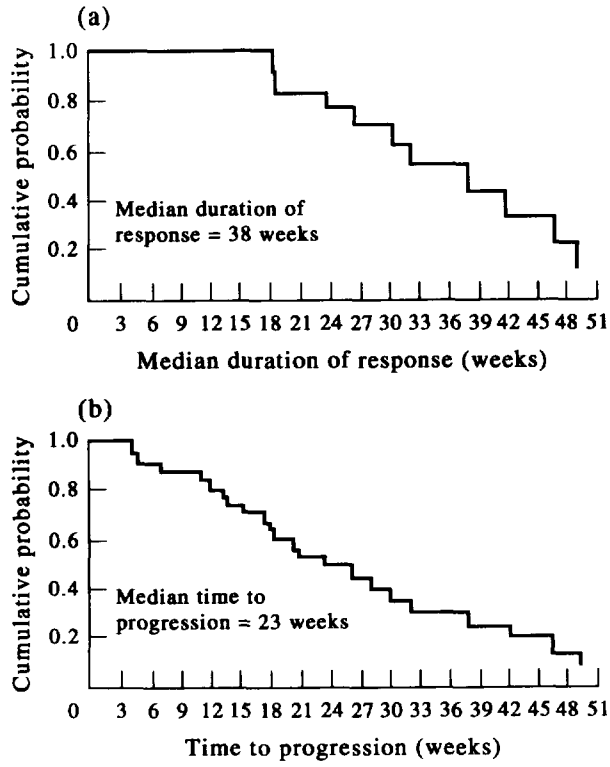

Figure 1. (a) Duration of response; and (b) time to progression in breast cancer according to the method of Kaplan–Meier. All evaluable patients were taken into account. Reproduced by permission of Kluwer Academic Publishers, from ten Bokkel Huinink W *et al.*, *Annals of Oncology* 1994, Vol. 5, pp. 527–532.

In the clinical trial context, progression-free survival is more or less the same as duration of response. This is more usefully measured than overall survival as a secondary endpoint in phase II trials, subject to the same reservations regarding patient demographics.

PROGRESS ARISING FROM CONVENTIONAL METHODOLOGY

After a period of lull, we are now seeing a variety of exciting new agents from a number of different drug classes under development. The taxoids, topoisomerase inhibitors and antimetabolites have all recently furnished us with highly promising agents through the results of conventional, high quality clinical research. An important example is the taxols. Docetaxel has activity against a number of different tumour types, and as a second-line drug in phase II studies, it has the highest single-agent activity ever documented in breast cancer, with an overall response rate of 58% [8] with the median duration of response at 38 weeks (Figure 1). In second-line treatment, as expected, the poorer patient prognosis shortens the median duration of response, but even in anthracycline resistant patients, the response duration was approximately 27 weeks.

Another taxoid showing promise in breast cancer and NSCLC is paclitaxel. A phase II study of paclitaxel as single-agent, second-line therapy of breast cancer produced responses

in 36% of patients who had received two prior treatments, and 21% of those who had received three prior treatments. Other studies involving heavily pretreated patients yielded overall response rates of up to 53% [9].

The topoisomerase I inhibitor, irinotecan, has also been tested in phase II trials and produced an overall response rate of 42% in previously treated patients with non-Hodgkin's lymphoma [10], 32% in untreated colorectal cancer [1] and greater than 20% in NSCLC [12].

Some agents from more established classes of drug are also producing promising results. For example, vinorelbine, a third generation vinca alkaloid, achieved an overall response rate of 30% when used as second- or third-line therapy for breast cancer [13]. Both vinorelbine and the antimetabolite, gemcitabine, have achieved response rates of 15–30% in NSCLC [14]. Oxaliplatin has shown good efficacy in a number of studies in advanced colorectal cancer [15].

Finally, it is worth noting that current evaluation methodology is also contributing to many improvements in combination chemotherapy schedules, as new agents with different modes of action become available.

CONCLUSION

The methods we currently use for assessing the efficacy of new anticancer drugs are the same ones that gave us the successes of the past, and they are now yielding promising new developments for the future. We must not discard them, but should continue to apply them with rigour.

1. Cvitkovic E, Spaulding J, Bethune V, Martin J, Whitmore WF. Improvement of *cis*-dichlorodiammineplatinum (NSC 119875): therapeutic index in an animal model. *Cancer* 1977, **39**, 1357–1361.
2. Schwartsmann G, Wanders J, Koier IJ, *et al.* EORTC New Drug Development Office coordinating and monitoring programme for phase I and II trials with new anticancer agents. *Eur J Cancer* 1991, **27**, 1162–1168.
3. Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer* 1981, **47**, 207–214.
4. *Practical Guide to EORTC Clinical Studies.* Therasse P, ed. EORTC Data Center, Brussels, 1996.
5. Abstracts of the XV ESMO Congress, Copenhagen: Melanomas. *Annals of Oncology* 1990, **1**, Suppl. V1.
6. Anderson GR, Cain KC, Gelber RD. Analysis of survival by tumor response. *J Clin Oncol* 1983, **1**, 710–719.
7. Neyt GB, ten Bokkel Huinink WW, Van der Burg MEL, *et al.* Long-term survival in ovarian cancer. Mature data from the Netherlands Joint Study Group for Ovarian Cancer. *Eur J Cancer* 1991, **27**, 1367–1372.
8. ten Bokkel Huinink WW, Prove AM, Piccart M, *et al.* A phase II trial with docetaxel (Taxotere) in second line treatment with chemotherapy for advanced breast cancer. *Ann Oncol* 1994, **5**, 527–532.
9. Seidman AD. Single-agent use of Taxol (paclitaxel) in breast cancer. *Ann Oncol* 1994, **5**, S17–S22.
10. Ohnishi K, Ohno R. New antitumor drugs for malignant lymphoma: a review. *Gan To Kagaku Ryoho* 1994, **21**, 1157–1162.
11. Conti JA, Kemeny EA, Saltz LB, *et al.* Irinotecan is an effective agent in untreated patients with metastatic colorectal cancer. *J Clin Oncol* 1996, **14**, 709–715.
12. Fukuoka M, Yoshikawa A. Therapeutic strategy for advanced non-small cell lung cancer. *Gan To Kagaku Ryoho* 1995, **22**, 37–44.
13. Fumoleau P, Delozier T, Extra JM, Canobbio L, Delgado FM, Hurteloup P. Vinorelbine (Navelbine) in treatment of breast cancer: the European experience. *Semin Oncol* 1995, **22** (Suppl. 5), 28–29.
14. Hansen HH. Have the new agents developed in the early 1990s changed the treatment of lung cancer. *Eur J Cancer* 1995, **31A** (Suppl. 5), S129.
15. Levi F, Machover D, Marty M, *et al.* Oxaliplatin (L-OHP): summary of results in advanced colorectal cancer. *Eur J Cancer* 1995, **31A** (Suppl. 5), S154.