Phase III trials in oncology

Setting standards of care?

Siegfried Seeber and Ada H Braun*

Survival data from phase III trials can be very misleading because patients are not offered the best follow-up therapy argue **Siegfried Seeber** and **Ada Braun** in *CancerWorld's* new Forum section. **Emma Mason** canvassed clinical trial leaders, and presents their responses in the Debate section that follows.

For many years, oncologists worldwide have advised their patients to enrol in clinical trials for optimum assessment of treatments, monitoring and follow-up, and consequently better survival and quality of life compared with routine management. Randomised phase III studies that have survival as the primary endpoint have been the indisputable basis for setting new standards and launching new drugs, combinations and multimodal treatment options into clinical oncology practice. Such studies may be misleading, however, when enrolled patients have not received optimum follow-up therapy after failure of the assigned treatment.

In recent licensing trials for agents targeted at breast cancer, restricted access to post-study chemotherapy has yielded 'superior' survival data for investigational drug combinations versus single-agent therapy, with remarkably poor survival in all cohorts.[1] A number of these trials have resulted in approval of specific regimens. In a study showing 'superior survival' for capecitabine plus docetaxel compared with docetaxel alone (14.5 vs 11.5 months, respectively) in 511 anthracycline-pretreated patients, only 17% of patients in the docetaxel-alone arm received post-study capecitabine, and overall only 30% received post-study vinorelbine and 20% 5-fluorouracil.[1] Especially given the very short median times to treatment failure reported (4.0 and 2.8 months), it is against routine practice to offer only two-thirds third-line chemotherapy. Capecitabine was consequently registered for breast cancer therapy, with docetaxel as the mandatory combination partner.

Gemcitabine was approved for combination therapy only, because a licensing trial comparing gemcitabine plus paclitaxel with paclitaxel alone stated that "gemcitabine plus taxol provides significant overall survival advantage over taxol."[2] The advantage of combination over sequential single-agent therapy is undetermined, however. Again, unsatisfactory post-study access to active agents probably accounted for the unacceptable median survival data reported (18.5 vs 15 months, respectively).

In a recent randomised trial of trastuzumab plus docetaxel in 188 patients with HER2-positive metastatic

* S Seeber is the Director of the West German Cancer Centre, and AH Braun is a Clinical Fellow at the West German Cancer Centre, University of Duisburg-Essen Medical School, Essen, Germany. AH Braun is also Research Instructor at Vanderbilt University, Nashville, Tennessee.
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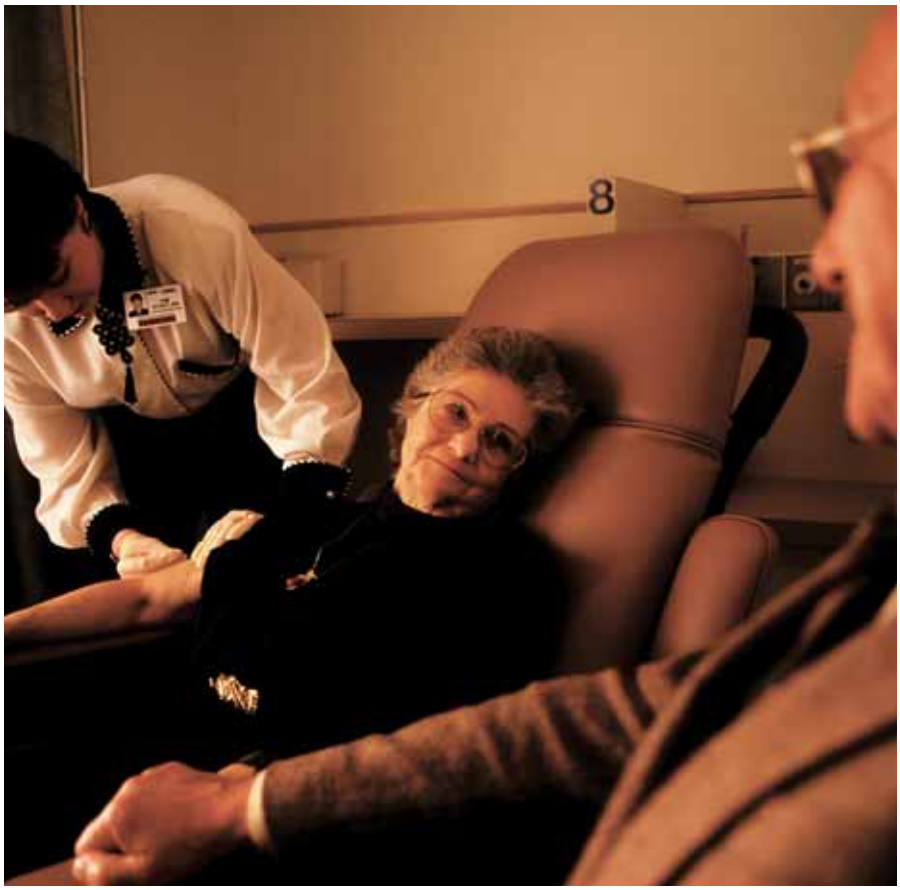

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breast cancer, only 48% of the taxotere-alone control group were documented to receive the antibody at progress! Yet it was concluded that the addition of trastuzumab to docetaxel "improves all clinical outcome parameters, including survival."[3] Would this hold true if patients from the control group had received vinorelbine plus trastuzumab after taxotere failure? Albeit active, the latter combination is still 'illegal'.

Should such studies set new standards of care for our patients? For 197 unselected consecutive patients treated in our centre in the pre-trastuzumab era (between 1 January 1995 and 31 December 1999), the median survival of breast cancer patients first-line for treatment of metastatic disease was 36 months, with a 35% four-year survival (C Pohlkamp, A Welt and S Seeber, unpublished data). Of 146 patients with inoperable liver metastases, 25% survived for over 48 months, and 14% for over 60 months – some for over eight years. In many cases, clinical responses were observed even in the sixth or seventh line (see Case Report, opposite). These patients require close monitoring, early intervention at progression, and individualised multimodal therapy employing effective drugs either singly or in adequate combinations, irrespective of their registration status. Dose-dense regimens should be used in critical phases and 'softer' interims involving oral maintenance therapy as well as locoregional treatment options (e.g. surgery, interventional radiology or hepatic artery infusions). Experienced physicians are not impressed by studies claiming a survival advantage of 15.4 vs 12.7 months for docetaxel versus paclitaxel in metastasised breast cancer,[4] a result advertised as a 'highlight' of the 2003 ECCO.

In stage 4 non-small-cell lung cancer, it took 408 patients to prove that combining paclitaxel with carboplatin is as effective as vinorelbine plus cisplatin,[5] with equally poor median survival (8 months), and one-year survival rates (38% vs 36%). In this and a similar ECOG (Eastern Cooperative Oncology Group) trial of four two-drug combinations, there was no routine crossover at treatment failure; nor did the majority of patients receive adequate second-line or third-line treatment. However, second-line taxotere can prolong life in platinum-refractory patients, and even third-line irinotecan can induce significant responses lasting up to one year.[6]

Unsatisfactory post-study access to active agents may account for the unacceptable median survival

Representative case report: breast cancer

57-year-old female patient with metastatic breast cancer; history of 15 lines of chemotherapy; now good performance status
Note that the patient has been treated off-label since the 2nd line of chemotherapy; alopecia was induced only under EC- (epirubicin/cyclophosphamide) and taxane-based treatment; response to treatment was assessed at least every 3 weeks using ultrasonography and serum markers (including CA 15-3 and LDH) or at least every 9–12 weeks using CT, MRI and/or X-rays; pulmonary metastases remained in good partial remission throughout treatment; any attempt to ascribe the relative contribution of individual drugs to the overall survival of the patient appears absurd.

09/1993	First diagnosis of breast cancer (invasive ductal adenocarcinoma; left breast) T1 N1 (2/11) M0; G2; oestrogen/progesterone receptor (ER/PR) negative; HER2+++ (immunohistochemistry) breast-conserving surgery, adjuvant radiotherapy left breast, 6 cycles of adjuvant chemotherapy (CMF; cyclophosphamide, methotrexate, 5-fluorouracil) in a peripheral hospital
09/1994	Increase in CA 15-3 tumour marker, indicative of relapse
07/1995	Total mastectomy on local recurrence; tumour now ER+, PR-; adjuvant tamoxifen therapy
01/1996	Once again increase in CA 15-3 tumour marker; first diagnosis of pulmonary metastases; treatment with the aromatase inhibitor formestane
12/1997	Progression of pulmonary metastases; first diagnosis of liver and bone metastases
01/1998	Treatment with the progestin medroxyprogesterone acetate (MPA) to no avail
04/1998	Chemotherapy with epirubicin and cyclophosphamide (EC; 1st line chemotherapy for metastatic disease); clinical response for more than 6 months
03/1999	Upon patient request of hair-sparing therapy, treatment with vinorelbine and 5-fluorouracil within a clinical trial (2nd line; until 09/1999); good clinical response
03/2000	Radiotherapy of right ileosacrum for pain control (30 Gy)
04/2000	Increase in CA15-3; docetaxel (3rd line) results in partial remission of hepatic lesions
10/2000	Bridging therapy with the aromatase inactivator exemestane proved to be ineffective
12/2000	Raf kinase inhibitor (BAY 43-9006; 4th line; phase I clinical trial); minor response for 5 months with excellent quality of life
06/2001	Fulminant hepatic disease progression (CA 15-3 increase up to 18,750); 3x monthly locoregional therapy (hepatic artery infusions) with mitomycin C plus 5-fluorouracil (5th line); major response and recovered performance status
09/2001	Oral maintenance therapy using capecitabine (6th line)
06/2002	Progressive disease (liver); oral chemotherapy with CMP (cyclophosphamide, methotrexate, prednisone; 7th line) induces partial response for 2 months
08/2002	Increase in CA 15-3; mitoxantrone therapy (8th line); clinical response for 3 months
11/2002	Increase in CA 15-3; combination therapy with vinorelbine and epirubicin (9th line)
12/2002	Although minor remission of hepatic lesions, due to toxicity therapy is continued with gemcitabine (10th line); time to disease progression is 3 months
03/2003	Trastuzumab (11th line) induces regression of hepatic and pulmonary lesions
09/2003	Tumour marker turnaround; treatment with vinorelbine (12th line)
01/2004	Oral capecitabine maintenance therapy (13th line)
06/2004	Upon marker progression, treatment with oral CMP (cyclophosphamide, methotrexate, prednisone; 14th line)
09/2004	Progressive disease (liver, pelvis, ascites); treatment with paclitaxel single-agent (15th line)
10/2004	Despite clinical response, change of therapy due to toxicity (polyneuropathy); docetaxel (16th line) induces minor response
12/2004	Since 12/2004, treatment paused; ultrasonography shows continued response but evidence of developing liver cirrhosis; good performance status (WHO 1)

In ovarian cancer, evidence-based medicine usually favours taxol plus carboplatin as induction treatment, with topotecan or liposomal doxorubicin for platinum-resistant tumours. Phase III studies are underway with overall survival as the primary endpoint.[7] Our mono-institutional analysis involves 77 unselected consecutive patients with FIGO stage 3 or 4 ovarian carcinoma, who, between 1 January 1993 and 31 December 2003, received an average of six treatment regimens, and early surgical interventions whenever applicable (C Brinkmann, J Hense and S Seeber, unpublished data). Therapies were adjusted on an individualised basis following any signs of disease progression, producing a median overall survival of 55 months in the total population and 63 months in stage 3 patients. Early adaptation of treatment regimens is mandatory for good patient outcome, and therapeutic interventions can prolong good-quality survival even late in the disease course.

Increasing evidence suggests that chemotherapy in hormone-refractory prostate cancer improves both quality of life and survival. Tannock et al.[8] examined docetaxel plus prednisone and mitoxantrone plus prednisone in such patients. Disconcertingly, they reported "superior survival" for the docetaxel arm, while crossover therapy after mitoxantrone failure was documented in only 20% of patients, with no other follow-up treatments specified. In our experience, second-line or third-line drugs can induce valuable responses over several months (A Schneider and S Seeber, unpublished data). Hence, the issue is not whether a mitoxantrone- or a taxane-based combination alone improves patient outcome, but which combinations or sequences are most rational.

Even colorectal cancer patients have suffered inferior survival in phase III studies because of constrained second-line treatment options. Goldberg et al.[9] reported that IFL (irinotecan, 5-fluorouracil and leucovorin) first-line therapy (also known as the Saltz regimen) was inferior to the FOLFOX regimen (oxaliplatin, 5-fluorouracil and leucovorin), but most patients enrolled in the study did not receive second-line oxaliplatin. Tournigand et al.,[10] comparing FOLFOX6 followed by FOLFIRI (irinotecan, infusional 5-fluorouracil and leucovorin) with the reverse sequence using a crossover design, found no significant difference in survival.

In conclusion, survival of patients with common metastatic cancers is determined not only by the choice of first-line chemotherapy regimen but also by sequentially applied alternative treatments at progression or relapse. Phase III trials documenting superior survival for any given primary chemotherapy in these diseases often offer patients insufficient access to salvage treatment and are therefore misleading. Unfortunately, results emanating from such studies continue to give rise to restricted licensing of mandatory drug combinations, even though physicians need both monotherapeutic and combined usage of active agents, according to a patient's history and preference – especially in advanced metastatic disease.

References
1. O'Shaughnessy J et al. (2002) Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J *Clin Oncol* 20:2812–2823
2. Albain KS et al. (2004) Global phase III study of gemcitabine plus paclitaxel (GT) vs paclitaxel (T) as frontline therapy for metastatic breast cancer (MBC): First report of overall survival. *Proc Am Soc Clin Oncol* 22:a510
3. Bell R et al. (2004) Maximizing clinical benefit with trastuzumab. *Semin Oncol* 31: 35–44
4. Ravdin P et al. (2003) Phase III comparison of docetaxel (D) and paclitaxel (P) in patients with metastatic breast cancer (MBC). *Eur J Cancer* Suppl 1:S201
5. Kelly K et al. (2001) Randomized phase III trial of paclitaxel plus carboplatin versus vinorelbine plus cisplatin in the treatment of patients with advanced non-small-cell lung cancer: a Southwest Oncology Group trial. J *Clin Oncol* 19:3210–3218
6. Schneider A et al. (2004) Weekly irinotecan in patients with advanced non-small-cell lung cancer (NSCLC) after failure of cisplatin, taxane and gemcitabine based chemotherapy. *Onkologie* 27 (Suppl 3):aP622
7. Du Bois A et al. (2004) Epirubicin/paclitaxel/carboplatin (TEC) vs paclitaxel/carboplatin (TC) in first-line treatment of ovarian cancer (OC) FIGO stages IIB-IV. An AGO-GINECO Intergroup phase III trial [abstract]. *Proc Am Soc Clin Oncol* 22:a5007
8. Tannock IF et al. (2004) Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med* 351:1502–1512
9. Goldberg RM et al. (2004) A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. J *Clin Oncol* 22:23–30
10. Tournigand C et al. (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 22:229–237

Early adaptation of treatment regimens is mandatory for good patient outcome

THE DEBATE

The central charge of the Seeber and Braun article, that patients in phase III trials are offered insufficient access to the best follow-up treatment after the first one has failed, which consequently skews the overall survival data, is contested by other oncologists.

They say that it would be unethical for patients to be denied proper post-trial treatment, and that no physician would ever enter their patients into a trial if they thought that this would happen.

As their first example, Seeber and Braun refer to a 2002 trial of capecitabine (Xeloda) plus docetaxel (Taxotere) combination therapy in patients with advanced breast cancer. "Only 17% of patients in the docetaxel-alone arm received post-study capecitabine, and overall only 30% received post-study vinorelbine and 20% 5-fluorouracil.

"Especially given the very short median times to treatment failure reported (4.0 and 2.8 months), it is against routine practice to offer only two-thirds of patients third-line chemotherapy," write Seeber and Braun.

Seeber told *CancerWorld*: "We … think that a number of recent registration studies do have an ethical problem, and it is by no means understandable that, for instance, in the Xeloda plus Taxotere versus Taxotere alone trial, only a small part of these patients received a crossover or adequate other therapies, although time to progression was very short."

However, Patrick Therasse, director of the data centre at the European Organisation for Research and Treatment of Cancer (EORTC), said: "The situation Seeber is referring to is a fact of life for cancer patients, some of whom will indeed not tolerate a second- or a third-line treatment because of the rapid evolution of their disease or because of their performance status being too low. But this is seen both in clinical trials and outside trials.

"I disagree with his statement, and I don't see why a patient in a clinical trial would have less access to salvage treatment than a patient out of a trial. On the contrary, some patients may even benefit from a crossover and access an investigational treatment that would otherwise not be available to them.

"It would be totally unethical not to be able to offer a patient the best salvage treatment because he has been in a trial; so participation in trials does not decrease access to state-of-the-art salvage treatment. If any physician believed this to be so, there would be no patients entered in clinical trials."

Monica Castiglione, chief executive of the International Breast Cancer Study Group (IBCSG), based in Bern, Switzerland, agreed with Therasse. "I would be very surprised to know that patients did not receive proper treatment after treatment failure in the trials. I cannot imagine ethical committees allowing the conduct of a trial that is mandating for improper treatment after failure. The fact that 'only' two thirds of the patients received a third-line chemotherapy looks to me quite normal. We generally have a number of patients with very aggressive disease to whom we are not able to apply third-line treatment."

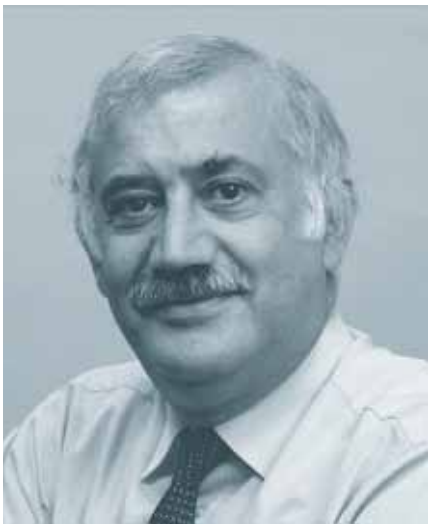
Seeber told *CancerWorld*: "During the trials the investigational drugs or combinations were superior regarding time to progression, but according to our experience these trials should not have reported survival gains. Survival in breast cancer, for example, is influenced by the long-term management, including often five and more lines of systemic treatment. In the papers we mentioned there was no satisfactory information on third-line therapies; most probably they had not been done. Indeed only 48% of the patients did receive trastuzumab when their tumours progressed."

But Castiglione said: "There are no data to my knowledge showing a survival benefit for third-line treatments in metastatic breast cancer; so this argument may be quite weak."

She believes that Seeber and Braun's use of the example of prolonging the lives of advanced breast cancer patients with inoperable liver metastases by treating them with several lines of different therapies is, in itself, misleading.

Siegfried Seeber: A drug has to be helpful, but it is nearly impossible to relate overall survival to one drug or one combination

Aron Goldhirsch: Phase IIIs tell us which treatment is better overall. The care of individuals must be extrapolated from the results



Stan Kaye: Using overall survival as an endpoint may fail to take proper account of treatments for relapse

"At the IBCSG we have examined the survival of patients from the time of metastases, and we observed that obviously visceral metastases have a poor survival, but we all know some patients with liver metastases who have survived several years; CNS [central nervous system] metastases have the worst survival, but I have a patient who is now surviving the tenth year. But one case cannot change our policies. We all know some patients who responded to the sixth or seventh chemotherapy. This is also, by far, not the rule, and a number of patients die before you can apply the third or fourth chemotherapy."

In other words, good (or bad) cases, are not good foundations on which to build general rules.

Therasse said: "To demonstrate the efficacy of a new treatment, there is, as yet, no good alternative to robust, randomised phase III trials. Stating better outcome, based on a small institutional survey is dangerous. The role of each clinician and investigator is to ask for more research when this is appropriate (and this is not always justified)."

Aron Goldhirsch, a member of the ethics committee of the European Institute of Oncology, Milan, Italy, said that the Seeber and Braun paper showed "significant confusion between 'on average this treatment is good for you' and knowledge about benefit of treatment for individuals."

He continued: "Phase III trials in oncology typically ignore individual patient care. They are focused on generating evidence on which treatment is better overall. The care of individual patients must be extrapolated from the trials' results; an exercise which is fruitful if selected predictive features are identified (i.e. tailored trials)."

Seeber and Braun suggest that if phase III trials were designed so that overall survival was not their primary endpoint and patients were able to access the best salvage treatment, this would help to prevent trials being "misleading", would prevent restrictive licensing of drugs and drug combinations, and would give patients access to the best salvage treatment after the end of the trial. "Unfortunately, results emanating from such studies [with overall survival as their endpoints] continue to give rise to restricted licensing of mandatory drug combinations, even though physicians need both monotherapeutic and combined usage of active agents, according to a patient's history and preference – especially in advanced metastatic disease," they write.

They say that, as things are at present, doctors are limited by restrictive licensing when considering further treatments if the cancer progresses, and this results in patients receiving less than optimum care.

"Our main point is: allow registration according to study endpoints of improved relapse-free survival or improved time to progression in the different clinical situation," said Seeber. "A drug has to be helpful, but it is nearly impossible to relate overall survival to the action of one drug or

Monica Castiglione: The fact that 'only' two thirds of the patients received a third-line chemotherapy looks quite normal

Patrick Therasse: If physicians thought participation in a trial decreased access to best salvage treatment, no patients would be entered

one combination."

Stan Kaye, professor of medical oncology at the Institute of Cancer Research, the Royal Marsden Hospital, UK, commented: "In principle, it is reasonable to say that phase III trials which use overall survival as an endpoint may fail to take proper account of treatments for relapse, which may be improving in several tumour types. This argues in favour of using progression-free survival as a better endpoint in phase III trials of initial therapy, and regulatory authorities now accept this." *

Castiglione also believes that drugs for metastatic disease should be registered on the basis of results from trials using endpoints of improved relapse-free survival or improved time to progression. But she agrees with Kaye that this is no longer an issue. "Regulatory authorities now accept progression-free survival and other endpoints for trials of metastatic diseases, and they accept disease-free survival for adjuvant trials. So I do not believe that this is a problem."

Goldhirsch is more cautious. "Who is the 'winner' mentality governs the marketing of several treatments, with single drugs or with combinations. Even if regulatory agencies will recognise a more sensitive endpoint, the essence of how marketing determines treatment choice will hardly change."

As to whether restricted licensing adversely affects our understanding about which are the most effective combinations or sequences of second, third or more lines of therapies, Therasse said: "There are many trials addressing these questions of treatment sequence and indications – probably too many as compared to other important questions which will remain unanswered, because there is no drug or no company behind them."

In conclusion, the scientists quoted above all disagree with Seeber and Braun that current phase III trial practice offers patients insufficient access to the best follow-up therapies. There is a general consensus that overall survival is not necessarily the best primary endpoint for a trial and that progression-free survival or improved time to relapse are more sensitive endpoints. However, Therasse and Castiglione believe that this is no longer a problem and that regulatory authorities accept these different endpoints.

The scientists questioned for this article did not think that current practice restricts our understanding of drug combinations or sequences for follow-up therapy, though the manner in which drugs are subsequently marketed was seen as unhelpful. Everyone believed that, at present, drug licensing has to be based on the evidence from large, randomised phase III trials.

The Debate was compiled by **Emma Mason**

WHAT DO YOU THINK?

CancerWorld would like to know what your thoughts or experiences are on these issues. Is there a problem with the way phase III trials are run and their effect on the way drugs are licensed? Do patients suffer from lack of proper follow-up treatment at the end of their trials? Contact us at editor@esoncology.org and let us know.

*The European Medicines Agency's Guideline On The Evaluation Of Anticancer Medicinal Products In Man, which gives details about their policy on crossover and use of overall survival versus disease-free or progression-free survival as a primary endpoint, can be found at www.emea.eu.int/pdfs/human/ewp/020595en.pdf