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Phase III trials in oncology: setting standards of care?

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For many years, oncologists worldwide have advised their patients to enroll in clinical trials for optimum assessment of treatments, monitoring and follow-up, and consequently better survival and quality of life compared with routine management. Randomized 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 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% 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, respectively), it is against routine practice to offer only two-thirds of patients 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 randomized trial of trastuzumab plus docetaxel in 188 patients with HER2-positive metastatic 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 center 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% 4-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 8 years. In many cases, clinical responses were observed even in the sixth or seventh line (see Supplementary Figure 1 online). These patients require close monitoring, early intervention at progression, and individualized 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 versus 12.7 months for docetaxel versus paclitaxel in metastasized breast cancer,[4] a result advertised as a "highlight" of the 2003 ECCO.

In stage IV 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 1-year survival rates (38% vs 36%). In this and a similar ECOG 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 third-line irinotecan can induce significant responses lasting up to 1 year.[6]

In ovarian cancer, evidence-based medicine usually favors taxol plus carboplatin as induction treatment, with topotecan or liposomal doxorubicin for platinum-resistant tumors. 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 III or IV 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 individualized basis following any signs of disease progression, producing a median overall survival of 55 months in the total population and 63 months in stage III 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 (see Supplementary Figure 2 online).

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) (see Supplementary Figure 3 online). 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 first-line therapy was inferior to the FOLFOX regimen, but most patients enrolled in the study did not receive second-line oxaliplatin. Tournigand *et al.*,[10] comparing FOLFOX6 followed by FOLFIRI 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.

Supplementary information is available on the *Nature Clinical Practice Oncology* website.

GLOSSARY

ECCO
European Cancer Conference

ECOG
Eastern Cooperative Oncology Group

FIGO
International Federation of Gynecology and Obstetrics

IFL
Also known as the Saltz regimen; standard therapy for colorectal cancer patients consisting of irinotecan, 5-fluorouracil and leucovorin

FOLFOX
Chemotherapy regimen for colorectal cancer patients consisting of oxaliplatin, 5-fluorouracil and leucovorin

FOLFIRI
A standard chemotherapy regimen for colorectal cancer patients consisting of irinotecan, infusional 5-fluorouracil and leucovorin

Competing interests
The authors declared they have no competing interests.

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