PERGAMON

European Journal of Cancer 38 (2002) 1957–1960

European Journal of Cancer

www.ejconline.com

Editorial Comment

Improved survival in advanced breast cancer with docetaxel and capecitabine in combination: biological synergy or an artefact of trial design?

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Received 17 May 2002; accepted 22 May 2002

Despite advances in the earlier detection and management of symptomatic disease over the past decade, there is a major need for more effective treatment for women with metastatic breast cancer. Adjuvant chemotherapy regimens now routinely incorporate anthracyclines, with taxanes used in the metastatic setting following anthracycline failure. An important paper in the *Journal of Clinical Oncology* has for the first time identified a combination chemotherapy superior to single-agent docetaxel [1]. O'Shaughnessy and colleagues [1] report that the combination of docetaxel and the oral fluoropyrimidine carbamate capecitabine (Xeloda) significantly prolongs survival compared with docetaxel alone in women with metastatic breast cancer previously treated with an anthracycline. Capecitabine is, of course, active in women with advanced breast cancer previously treated with a taxane [2] and licensed in many parts of the world, with the notable exception of the European Community. Many clinicians would consider treatment with a taxane followed by capecitabine as the current 'gold standard' for women with HER-2 negative tumours. This new study raises the question of whether we should adopt combination therapy rather than a sequential treatment approach.

In looking at these new data, it is useful first to set them in context. For many years, it was unclear to what extent systemic chemotherapy affected the survival of women with metastatic breast cancer. It is now clear that survival can be improved, with both vinorelbine (Navelbine) superior to melphelan (Alkeran) [3] and docetaxel (Taxotere) superior to the combination of mitomycin C and vinblastine [4]. More recently, the addition of the monoclonal antibody trastuzumab (Herceptin) to chemotherapy resulted in prolonged survival compared with chemotherapy alone [5]. In many other studies, however, improved response rates and time to progression have not translated into prolonged survival [6–11]. This 'failure' has been variously attributed to the dynamics of tumour growth, lack of statistical power and the confounding effects of subsequent treatment. In particular, cross-over to the more active treatment arm may abrogate any initial benefit in response and time to progression, so that overall survival is unaltered. The corollary of that argument is that the *absence* of such cross-over may create the spurious impression that a treatment is superior.

The complexities of interpreting clinical trial data are highlighted by the paper from O'Shaughnessy and colleagues [1]. This phase III trial in 511 women with anthracycline pretreated metastatic breast cancer compared the current optimal treatment with docetaxel 100 mg/m^2 to the combination of docetaxel 75 mg/m^2 and capecitabine 1250 mg/m^2 twice daily on days 1–14 of a 21-day cycle. The combination not only achieved a higher response rate (42% versus 30%, $P=0.006$) and median time to progression (6.1 versus 4.2 months, $P=0.0001$), but also significantly prolonged survival (median 14.5 versus 11.5 months, $P=0.0126$). The two treatment arms had differing patterns of toxicity, with myelosuppression prominent for single-agent docetaxel whereas diarrhoea and hand–foot syndrome were more

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PII: S0959-8049(02)00167-3

common with the combination. Overall quality of life was certainly no worse for those women receiving docetaxel and capecitabine in combination.

So, should the combination of docetaxel and capecitabine be considered a new 'gold standard' for women with anthracycline pretreated breast cancer? Individual oncologists and their patients will judge issues of activity, toxicity and quality of life, but the trial raises another question that has broader implications: Is combination chemotherapy *per se* superior to sequential, single agent treatment? In this trial, a similar percentage of women on the single agent and combination treatment arms received poststudy chemotherapy (70 and 63%, respectively), but only 17% of the women treated first with docetaxel alone went on to receive capecitabine [1]. The question of whether the combination of docetaxel and capecitabine provides superior survival over sequential treatment cannot, therefore, be directly answered by this trial.

The trial reported by O'Shaughnessy and colleagues [1] has, however, generated other interesting information potentially relevant to this question. A retrospective analysis suggested that treatment with capecitabine following docetaxel may indeed be an effective 'salvage' therapy. Women randomised to single agent docetaxel had a median survival of 21.0 months if they later received capecitabine, compared with 12.3 months for those who subsequently received other chemotherapy [12]. This equated to a significantly lower risk of death for women who subsequently received capecitabine rather than other cytotoxic treatment ($P = 0.005$). These data suggest that sequential chemotherapy with docetaxel followed by capecitabine is particularly active. However, it is striking that the published survival curve for docetaxel and capecitabine separates from the single agent docetaxel curve early which argues for the initial use of the combination regimen.

Other indirect evidence to support the combination of docetaxel and capecitabine comes from preclinical studies demonstrating synergy [13]. Capecitabine is converted to 5-fluorouracil (5-FU) by a series of enzymes, the final one being thymidine phosphorylase (TP) which is more active in malignant than normal tissues. Docetaxel further upregulates TP expression in tumours [14] which may generate more 5-FU within the cancer, leading to clinical synergy. This provides a rationale for this particular combination having genuine advantages over sequential single-agent treatment. Other preclinical evidence of synergy between capecitabine and docetaxel independent of changes in TP expression suggests, however, that the nature of this interaction has yet to be fully defined [15].

The trial from O'Shaughnessy and colleagues [1] was not designed to address the combination versus sequential treatment question and neither additional analyses nor preclinical data can fully resolve this issue for clinicians. What then can we learn about the importance of cross-over from other trials where the issue of treatment sequence arises? Table 1 summarises results of trials where there was benefit in time to progression and/or response rate, for which cross-over data can be interpreted. In addition to the results from O'Shaughnessy and colleagues [1], three other chemotherapy-based trials in women with metastatic breast cancer showed a significant improvement in survival. The trial comparing vinorelbine with melphelan did not allow cross-over [3], whereas when docetaxel was compared with mitomycin and vinblastine cross-over occurred in 12 and 24% of patients, respectively [4]. In the trial of chemotherapy with or without trastuzumab, 66% of the women who initially received chemotherapy alone went on to receive trastuzumab (with or without further chemotherapy) at progression [5]; despite this, survival was significantly longer in women randomised to receive chemotherapy with trastuzumab as their initial therapy.

Table 1
Summary of trial results

Regimen (Ref.)	No. pts entered	RR (%)	TTP (months)	OS (months)	Cross-over to more active regimen (%)
Significant survival benefit observed					
Docetaxel/capecitabine versus docetaxel [1]	511	42/30*	6.1/4.2*	14.5/11.5*	17
Vinorelbine versus melphelan [3]	183	46/28*	2.8/1.9*	8.1/7.2*	Not allowed
Doxorubicin versus MMC/vinblastine [4]	392	30/12*	4.4/2.5*	11.4/8.7*	24
Doxorubicin/cyclophosphamide or paclitaxel, ± trastuzumab [5]	469	50/32*	7.4/4.6*	25.1/20.3*	66
No significant survival benefit					
Doxorubicin versus paclitaxel versus combination [11]	739	34/33/46*	6.2/5.9/8.0*	20.1/22.2/22.4	Planned for all
Doxorubicin versus paclitaxel [10]	331	41/25*	7.5/3.9*	18.3/15.6	40 (75% of those eligible)
Docetaxel versus doxorubicin [9]	326	48/33*	6.0/4.8	15/14	26
Doxorubicin versus methotrexate→5-FU [8]	267	42/21*	6.3/3.0*	10.4/11.1	28

RR, response rate; TTP, time to progression; OS, overall survival; MMC, mitomycin C; pts, patients; 5FU, 5-fluorouacil.
* Significant difference.

Clearly, cross-over does not necessarily preclude translating an improved response rate or time to progression into a survival benefit. Nevertheless, several of the trials that were 'negative' in terms of survival were characterised by rates of cross-over higher than that reported by O'Shaughnessy and colleagues [1]. With cross-over as part of the study design, the combination of doxorubicin and paclitaxel achieved a significantly higher response rate and longer time to treatment failure than either drug as a single agent, but there was no difference in survival [11]. Preliminary results from another small study with planned cross-over, this time with docetaxel, are similar [16]. Likewise, in other trials with cross-over rates of 26, 28 and 75% significant benefits in terms of response rate [8–10] or time to progression [8,10] did not lead to improved survival.

Putting the clinical trial data together, the evidence that combination treatment is inherently superior to sequential treatment is not strong. The evidence favouring combination therapy is best for paclitaxel with trastuzumab [5], and docetaxel with capecitabine [1]. In both cases, the agents combined are distinct in their mode of action and may demonstrate genuine synergy. In the context of metastatic breast cancer, the case for combining the most active single agents is much less strong with other cytotoxics. With the trial from O'Shaughnessy and colleagues [1] in mind, perhaps the most provocative comparison is with another study investigating the addition of an active drug, vinorelbine, to standard single-agent treatment with doxorubicin [17]. In this trial, the combination of doxorubicin and vinorelbine was more toxic and there was no improvement in the response rate or time to progression with the allocated therapy. Likewise, when paclitaxel was compared with cyclophosphamide as a partner for doxorubicin, increased toxicity and a consequent loss of delivered doxorubicin dose intensity resulted in there being no impact on the response rate or other measures of efficacy [18]. Clearly, simply combining cytotoxics with proven single-agent activity does not necessarily lead to improvement even in terms of response rate.

We should not, therefore, dismiss improvements in survival even where lack of cross-over complicates interpretation of the data. In the trial reported by O'Shaughnessy and colleagues [1], the low rate of cross-over will certainly have maximised the survival benefit. This is not, however, sufficient reason to ignore the clear improvement in survival seen with the combination. With capecitabine now licensed for use both as a single agent and in combination with docetaxel, there is no regulatory requirement formally to address the question of combination versus sequential therapy. Mandatory cross-over in trials is feasible, as shown by the studies of sequential versus combination therapy with doxorubicin and paclitaxel [10,11], but would be difficult in pivitol trials if the new agent is not yet licensed, as was the case for capecitabine. The question of treatment sequence is important and may still be an issue for collaborative trials groups to address. However, it may be naïve to expect a 'one size fits all' answer and clinical investigators may well consider questions such as the optimal scheduling of docetaxel and capecitabine [15], or identifying sub-groups of patients most likely to benefit from the combination according to the biochemical profile of their tumours as a higher priority [19].

For the practising oncologist and women with breast cancer, it probably matters most that this trial increases the range of effective treatment options than that we cannot be sure how much of the improvement in survival is a consequence of the trial design. There is good reason to believe that there may be synergy in the combination of docetaxel and capecitabine, both from the strength of the clinical data and also from laboratory models of synergy. In women with anthracycline-resistant, HER-2-negative metastatic breast cancer if the priority is to maximise their chance of response and prolong survival, optimal chemotherapy would be with the combination of docetaxel and capecitabine. For women for whom the combination is not appropriate, or who want a less intensive treatment, docetaxel followed by capecitabine is a very reasonable alternative.

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