Extending the duration of first-line chemotherapy in metastatic breast cancer: a perspective review

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***Abstract*:** The treatment of metastatic breast cancer is mainly palliative, but optimal management might result in survival improvement as well. For this reason, many trials have attempted to optimize the therapeutic approach in this disease setting. Among the possible options, chemotherapy represents the backbone of the treatment and survival improvements that have been shown by the use of modern chemotherapeutic agents. Whereas the type of chemotherapy is generally dictated by patient characteristics and those of their disease, substantial controversy still remains on how long chemotherapy should be administered after disease control is achieved. In this review, we have analysed all available evidence on the duration of first-line chemotherapy in advanced breast cancer.

***Keywords*:** chemotherapy, duration, metastatic breast cancer, overall survival, progression-free survival

Introduction

The management of metastatic breast cancer is a major clinical challenge for medical oncologists. Indeed, in spite of all of the available agents, this stage of disease can rarely be cured. Therefore, therapeutic goals are palliative: prolongation of survival with good quality of life and control of symptoms are the primary objectives. However, it is important to recognize that patients with metastatic breast cancer are a heterogeneous group, and thus the aims of treatment will differ depending on the circumstances of the individual patient. For example, patients with symptomatic disease and poor performance status will benefit mainly from palliative treatment, while in many elderly patients with indolent disease the aim is to delay progression and improve quality of life. In contrast, in younger patients and those with good performance status, treatment should aim to prolong survival, whereas in patients whose disease is amenable to locoregional control the aim should be to increase response rates. In recent years, the introduction of a number of novel therapies for patients with metastatic breast cancer has resulted in marked improvements in survival [Chia *et al.* 2007; Gennari *et al.* 2005].

With respect to treatment choice, it can reasonably be assumed that virtually all patients with metastatic disease sooner or later will require chemotherapy. In particular, for patients with hormone receptor-negative or endocrine-resistant disease, cytotoxic chemotherapy is indicated [National Comprehensive Cancer Network, 2010].

Because it is possible to extend the survival of metastatic breast cancer patients, the relative benefit of therapy in causing tumour regression and improvement in disease-related symptoms must be balanced with treatment-induced toxicity and the impact upon the patient's quality of life.

Challenges in the management of metastatic breast cancer

Treatment choices for metastatic breast cancer include endocrine treatment, cytotoxic chemotherapy, nonendocrine targeted therapy, bisphosphonates, and supportive measures. The administration of endocrine therapy following chemotherapy in endocrine-responsive metastatic breast cancer is a common practice.

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This approach is biologically plausible, although there is insufficient evidence in the literature to support it. It should also be considered that patients with endocrine-responsive tumours, treated with first-line chemotherapy, have longer survival rates than patients with negative hormonal status [Bertelli *et al.* 2005].

Duration of first-line chemotherapy

The selection of optimum chemotherapy is influenced by the characteristics of the patient and her cancer as well as by her preferences and those of her physicians. There is, however, substantial controversy over how long chemotherapy should be extended, in the absence of significant toxicity, after the achievement of disease control. In this setting in fact, two different strategies may be recommended, according to treating physician preferences and his or her scientific background. The most conservative approach is to administer first-line chemotherapy for a fixed number of cycles, or until the 'best response' is achieved and then stop and offer the patient a 'chemo vacation', until the disease will be in progression again. The other approach is where no planned chemotherapy duration is foreseen and treatment is administered until disease progression or excessive toxicity.

In clinical practice, for patients allocated to receive first-line chemotherapy, the optimal decision making about whether to continue the treatment should be based on discussions between the patient and their treating physician: symptoms, side effects, quality of life, and preferences should be monitored and taken into account. Currently available evidence indicates that it may be reasonable to continue chemotherapy in the absence of disease progression or significant side effects.

Current guidelines state that there is limited evidence to suggest that progression-free survival can be prolonged by the use of continuous chemotherapy, rather than shorter courses, but due to the lack of effect on overall survival the detrimental impact of continuous treatment on quality of life should also be considered [National Comprehensive Cancer Network, 2010]. Thus, the duration of chemotherapy in an individual patient will depend on the efficacy and tolerability in that patient, and on the physician's and patient's preferences.

Over the past two decades, a number of clinical trials have addressed the issue of optimal chemotherapy duration in metastatic breast cancer [Alba *et al.* 2010; Mayodromo *et al.* 2009; Gregory *et al.* 1997; Gennari *et al.* 2006; Nooji *et al.* 2003; French Epirubicin Study Group, 2000; Falkson *et al.* 1998; Ejlertsen *et al.* 1993; Muss *et al.* 1991; Harris *et al.* 1990; Coates *et al.* 1987]. In 1997, the results of a meta-analysis [Stockler *et al.* 1997] of data abstracted from some of these studies indicated that the policy of prolonging treatment in the absence of progressive disease or treatment in the absence or progressive disease or unacceptable toxicity had a favourable impact on overall survival. In particular, this analysis, which included data from four studies involving 666 patients, indicated that median survival was increased by 23% (95% confidence interval [CI] 9–38%, $p = 0.01$) in women receiving longer durations of chemotherapy as compared with a limited number of cycles. However, some early studies, comparing different chemotherapy durations, were plagued by a number of limitations, such as insufficient sample size, limited chemotherapy administration in control arms, and/or drugs and scheduled that, based on today standards, can be considered obsolete. Conversely, the results of more recent trials addressing chemotherapy duration with new chemotherapeutic agents yielded inconsistent results.

Systematic review of chemotherapy duration in metastatic breast cancer

The impact of extending the duration of chemotherapy beyond a fixed number of cycles has recently been investigated in a systematic review of 11 randomized trials evaluating first-line chemotherapy in patients with metastatic breast cancer [Gennari *et al.* 2011]. Longer durations of chemotherapy were associated with a marginal increase in overall survival, equivalent to approximately 3 months (hazard ratio [HR] 0.91, 95% CI 0.84–0.99) and a significant prolongation of progression-free survival (HR 0.66, 95% CI 0.6–0.72), compared with shorter durations. No differences in effects on overall survival and progression-free survival among subgroups defined by time of randomization, study design, number of chemotherapy cycles in the control arm, or concomitant endocrine therapy was detected.

The impact of different chemotherapy durations of treatment on health-related quality of life was evaluated in one trial only [Coates *et al.* 1987].

In this study, continuous chemotherapy was associated with a better quality of life, compared with intermittent therapy; patients receiving continuous treatment showed also improved scores for physical wellbeing, mood, appetite, and general quality of life. Changes in quality of life were found to be independent predictors of subsequent survival.

Overall, these results indicate that strategies for extending first-line chemotherapy are associated with a clinically modest but statistically significant improvement in overall survival and a clinically meaningful and statistically significant improvement in progression-free survival. These results confirm and strengthen, with more recent evidence, data from the previous meta-analysis on chemotherapy duration, performed 7 years ago by Stockler and colleagues [Stockler *et al.* 2003], which showed a modest, but statistically significant survival advantage with longer chemotherapy administration, supporting a policy of prolonging treatment until disease progression, in the absence of unacceptable toxicity.

The more recent meta-analysis takes advantage of new trials not included in the previous study and particularly of studies with new cytotoxic agents and novel drug formulations and allowed more powerful comparisons of treatment effects, particularly in subgroup analyses.

As expected, the effect of prolonged chemotherapy was much more evident in terms of progression-free survival (HR, 0.64; 95% CI, 0.55–0.76) than of overall survival (HR, 0.91; 95% 0.84–0.99). However, despite the marginal effect of longer chemotherapy administration on overall survival, prolonging chemotherapy can be considered clinically worthwhile, because of the well-known effect of the prolongation of progression-free survival on quality of life [Geels *et al.* 2000].

Among the possible limitations of this new analysis, the most important is the fact that in some of the early studies, the tested chemotherapeutic regimens can be considered obsolete today and probably inferior to those used currently. Moreover, an analysis conducted on individual patient data, would have allowed a quality control on the original records and analyses, as well as the chance to perform additional subgroup analyses.

Despite these limitations, in a pragmatic perspective, this analysis quantifies the benefits associated with prolonged first-line chemotherapy in metastatic breast cancer and indicates that these benefits are particularly relevant in terms of progression-free survival, independently of many other factors including endocrine maintenance therapy.

Translation into clinical practice

After these results, in everyday clinical practice the patient should be therefore informed that they will likely get the best chance for an improved outcome with a longer chemotherapy administration. This approach must however be weighed against the detrimental effects of continuous chemotherapy delivery on patient quality of life.

In fact, the management of a patient with metastatic breast cancer needs to be tailored on the patient and their disease characteristics, and cannot even ignore the patient's needs and desires. For this reason, despite available evidence from the above reported meta-analysis supporting the policy of prolonging chemotherapy until disease progression or unacceptable toxicity, the correct approach is based on a solid patient–physician relationship to reach a common decision.

Another consideration is that in modern oncology practice, prolonging chemotherapy after disease control by the administration of full-dose chemotherapy may be considered an outdated concept and may not be feasible because of excessive toxicity and the impact on quality of life. As a matter of fact, when prolonging chemotherapy after disease control is reached, alternative schedules (i.e. lower/metronomic dosages and/or delayed administrations) are often used in the clinical practice.

Future research

Despite extensive research efforts, the optimal duration and type of prolonged chemotherapy schedules are far from being clearly defined. For this reason, in a scientific perspective, the new meta-analysis supports further research on maintenance therapy in metastatic breast cancer. In particular, new studies should investigate and further clarify the role of chemotherapy duration in association with targeted agents such as anti-HER2 and anti-angiogenetic drugs. This type of research could also explain the inconsistent results achieved in randomized clinical trials with targeted agents. Another possible

research field includes a study of the administration of sequential single chemotherapeutic agents, each for a planned number of cycles, in an attempt to avoid cumulative toxicities and drug resistance. Finally, prolonged chemotherapy schedules should be optimized with the evaluation of the efficacy of lower doses of active chemotherapeutic drugs, with a possible favourable impact on quality of life and survival.

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Conflict of interest statement

The authors declare no conflict of interest in preparing this article.

References

Alba, E., Ruiz Borrego, M., Margeli, M., Rodriguez-Lescure, A., Sanchez-Rovira, P., Ruiz, A., Mel-Lorenzo, J.R. *et al.* (2010) Maintenance treatment with pegylated liposomal doxorubicin *versus* observation following induction chemotherapy for metastatic breast cancer: GEICAM 2001-01 study. *Breast Cancer Res Treat* 122: 169–176.

Bertelli, G., Garrone, O., Bertolotti, L., Occelli, M., Conforti, S., Marzano, N. *et al.* (2005) Maintenance hormone therapy with letrozole after first-line chemotherapy for advanced breast cancer. *Oncology* 68: 364–370.

Chia, S.K., Speers, C.H., D'yachkova, Y., Kang, A., Malfair-Taylor, S., Barnett, J. *et al.* (2007) The impact of new chemotherapeutic and hormone agents on survival in a population-based cohort of women with metastatic breast cancer. *Cancer* 110: 973–979.

Coates, A.S., Byrne, M., Bishop, J.F. and Forbes, J.F. (1987) Intermittent *versus* continuous chemotherapy for breast cancer. *N Engl J Med* 314: 1490–1495.

Ejlertsen, B., Pfeiffer, P., Pedersen, D., Mouridsen, H.T., Rose, C., Overgaard, M. *et al.* (1993) Decreased efficacy of cyclophosphamide, epirubicin and 5-fluoracil in metastatic breast cancer when reducing treatment duration from 18 to 6 months. *Eur J Cancer* 29A: 527–531.

Falkson, G., Gelman, R.S., Pandya, K.J., Osborne, C.K., Tormey, D., Cummings, F.J. *et al.* (1998) Eastern Cooperative Oncology Group randomized trials of observation *versus* maintenance therapy for patients with breast cancer in complete remission following induction treatment. *J Clin Oncol* 16: 1669–1676.

French Epirubicin Study Group. (2000) Epirubicin-based chemotherapy in metastatic breast cancer patients: Role of dose intensity and duration of treatment. *J Clin Oncol* 18: 3115–3124.

Geels, P., Eisenhauer, E., Bezjak, A. *et al.* (2000) Palliative effect of chemotherapy: Objective tumor response is associated with symptom improvement in patients with metastatic breast cancer. *J Clin Oncol* 18: 2395–2405.

Gennari, A., Amadori, D., De Lena, M., Nanni, M., Bruzzi, M., Lorusso, V. *et al.* (2006) Lack of benefit of maintenance paclitaxel in first-line chemotherapy in metastatic breast cancer. *J Clin Oncol* 24: 3912–3917.

Gennari, A., Conte, P., Rosso, R., Orlandini, C. and Bruzzi, P. (2005) Survival of metastatic breast carcinoma patients over a 20-year period: a retrospective analysis based on individual patient data from six consecutive studies. *Cancer* 104: 1742–1750.

Gennari, A., Stockler, M., Puntoni, M., Sormani, M., D'amico, M., De Censi, A. *et al.* (2011) Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials. *J Clin Oncol*, ePub ahead of print.

Gregory, R.K., Powles, T.J., Chang, J.C. and Ashley, S. (1997) A randomized trial of six *versus* twelve courses of chemotherapy in metastatic carcinoma of the breast. *Eur J Cancer* 33: 2194–2197.

Harris, A.L., Cantwell, B.M., Carmichael, J., Wilson, R., Farndon, J., Dawe, P. *et al.* (1990) Comparison of short-term and continuous chemotherapy(mitozantrone) for advanced breast cancer. *Lancet* 335: 186–190.

Mayodromo, J., Baena, J.M., Cirera, P., Sanchez-Rovira, P., Godes, M.J., Galan, A. *et al.* (2009) Final results of a randomised trial on the role of maintenance chemotherapy with weekly paclitaxel for patients with metastatic breast cancer. *J Clin Oncol* 27: 41s, abstract 1001.

Muss, H.B., Case, L.D., Richards, F.II., White, D.R., Cooper, M.R., Cruz, J.M. *et al.* (1991) Interrupted *versus* continuous chemotherapy in patients with metastatic breast cancer: The Piedmont Oncology Association. *N Engl J Med* 325: 1342–1348.

National Comprehensive Cancer Network (2010) Practice guidelines in oncology, v.2. Breast cancer. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp.

Nooji, M.A., de Haes, J.C.J.M., Beex, L.V.A.M., Wildiers, J., Klijn, J., Becquart, D. *et al.* (2003) Continuing chemotherapy or not after the induction treatment in advanced breast cancer patients: Clinical outcomes and oncologists' preferences. *Eur J Cancer* 39: 614–621.

Stockler, M., Wilcken, N. and Coates, A. (1997) Chemotherapy for metastatic breast cancer – when is enough enough? *Eur J Cancer* 33: 2147–2148.

Stockler, M.R., Wilcken, N.J.C. and Coates, A.S. (2003) Chemotherapy for advanced breast cancer: How long should it continue? *Breast Cancer Res Treat* 81(Suppl. 1): S49–S52.