Short Report

CMF with 5-FU in continuous infusion – a pilot study

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In the past decades the cyclophosphamide, methotrexate, 5-fluoroucil (CMF) regimen was a widely used chemotherapy protocol for adjuvant breast cancer treatment and its efficacy has been soundly proven [1]. Since in colon and breast cancer [2] fluorouracil (5-FU) has demonstrated an enhanced efficacy when it is administered by continuous infusion (CI) attempts have been made to administer 5-FU CI along with CMF [3, 4]. More recently, anthracyclines and/or taxanes contaning protocols (ATcP) have become more used in patients with a poor prognosis. While CMF has practically disappeared in France and the USA it is still sometimes administered in Italy since it has not exactly been established which subsets of patients require more aggressive treatment. ATcP indeed cause more toxicity. In particular, it been should be remembered that the risk of cardiotoxicity with the use of anthracyclines also includes delayed heart failure and non symptomatic reduction in myocardial ejection.

We designed a revised schedule of CMF using 5-FU CI at larger doses than in past trials and with an original schedule.

In our version, CMF drug administration was as in the classical protocol on day 1, but on day 8 only the usual doses of cyclophosphamide and methotrexate were injected: from day 9 to day 22 5-FU CI was administered (the efficacy of this sequence has been demonstrated by Marsh *et al.* [5]) and the period of rest lasted from day 22 to day 28. We used a fluoropyrimidine dose of 250 mg/m^2/day in two patients, 300 mg/m^2/day in another two patients and 350 mg/m^2/day in a further six patients. 5-FU escalation was then stopped due to the appearance of mucosal dose-limiting toxicity.

Enrolled patients (aged 41-76) were in an adjuvant phase in seven cases, in an advanced phase of disease in two cases and in an adjuvant post-metastasectomy phase in one case. None of them had previously received CMF. Patients in the adjuvant setting displayed > 30 mo of disease-free survival (DFS), both patients in advanced phases achieved a partial response (PR) and the duration was 27 + mo, while the patient treated post-metastasectomy had a DFS of 42 months.

Though results seem to be encouraging these few cases do not allow any conclusion on the regimen effects. However, good activity is reasonably expected since, for the average patient, the delivered dose of 5-FU was 1830 mg per week vs 300 mg per week of the classical CMF. We wish instead to stress the feasibility and low toxicity of this protocol despite the higher 5-FU doses with respect to previous experiences [3, 4]. Never with the 5-FU dose of 350 mg/m^2/day did we observe severe adverse effects. They were acceptable with mucosal toxicity grade 1-2 in five patients and myelosuppression (thrombocytopenia grade 2) in two patients. Only one patient interrupted treatment due to severe oral aphthosis.

Overall in our experience CMF CI has been active and well tolerated. Its direct and indirect (toxicity management) mean cost is € 2,810 for six cycles. This cost is similar to that of six courses of 5-FU, epirubicin, cyclophosphamide (FEC) but much less than the € 9,468 needed for four courses of FEC + four courses of docetaxel in our hands.

If further studies confirm the good activity of this regimen, CMF CI, could be a suitable treatment to avoid major toxicity, especially in some subsets of patients such as the elderly, patients with cardiopathies and perhaps all patients at intermediate prognostic risk.

Key words: CMF; Breast cancer.

References

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