

## METRONOMIC CHEMOTHERAPY IN ELDERLY PATIENTS: DO RISKS EXCEED BENEFITS IN SOME PATIENTS?

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Oral chemotherapy sometimes shows good activity with reduced toxicity<sup>1</sup>; some agents, such as methotrexate and cyclophosphamide, have also a significant antiangiogenic effect in animal models<sup>2</sup>. On this basis, continuous treatment with oral low-dose methotrexate and cyclophosphamide in patients with metastatic and previously treated breast cancer showed activity and very low toxicity<sup>3</sup>. A study in the adjuvant setting (T1-3 N0+ M0 ER <10% and PgR <10%) for patients aged more than 66 years, with a schedule based on methotrexate 2.5 mg twice a day, 2 days weekly and cyclophosphamide 50 mg daily, both for 16 weeks, is under way<sup>4</sup>. However, in daily practice we sometimes face unexpected toxicity after a "safe" treatment. Here we report a dramatic example of this unfavorable occurrence.

An 84-year-old woman presented with ductal breast cancer with axillary and liver involvement (ER 0%, PgR <10%, Ki67 55%, C-erbB-2: 2+). She had a history of heart failure; ECOG performance status was 2 and liver function tests were mildly altered, whereas blood count and kidney tests were normal.

After a comprehensive geriatric assessment she was considered "frail"<sup>5</sup> but, on the basis of the previous considerations on safety and efficacy, we started metronomic treatment with methotrexate 2.5 mg twice a day, 2 days weekly and cyclophosphamide 50 mg daily. Three days after the start of therapy, the patient experienced asthenia, diarrhea and nausea. Treatment was interrupted and the patient was admitted to hospital. On the first day of admission we documented a decline in

performance status with acute renal failure, hyperkalemia, bowel obstruction, grade 1 leukopenia, and mild alteration of liver tests. On the following day we observed severe myelotoxicity (grade 4 neutropenia, grade 1 anemia, platelets in the lowest range of normality). Despite supportive care with aggressive hydration, G-CSF and antibiotics, her clinical condition worsened. On day 7 her blood count was as follows: leukocytes 530 10<sup>3</sup>/mcl (neutrophils 20), platelets 2000 10<sup>3</sup>/mcl, Hb 8.3 g/dL; creatinine was 2.4 mg/dL and bilirubin 5.9 mg/dL (conjugated 4.3). On day 8 the patient died.

This unexpected and dramatic course raised some doubts about the safety of this combination. However, in the literature we did not find any report of such severe toxicity with this schedule. A mistake in the doses and/or number of days of administration was excluded by the relatives, even though in the outpatient setting some doubts regarding patient compliance could be justified. We could not explain this abnormal toxicity with drug interactions either, because the patient was not taking medications known to interact with methotrexate or cyclophosphamide (allopurinol, cimetidine, phenobarbital, indomethacin, diphenylhydantoin, neomycin, tetracycline, salicylates), nor herbal medicines.

As a possible explanation we can hypothesize an abnormal and genetically determined sensitivity to these chemotherapy agents, probably due to the presence of enzymatic isoforms (for example cytochrome P-450) with altered activity, resulting in enhanced activation or reduced catabolism of the drugs.

### References

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Received February 1, 2007; accepted March 20, 2007.