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A Rapidly Progressing Leiomyosarcoma Expressing Drug-resistance Markers Failed to Respond to Cyclosporin A-associated Chemotherapy

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PROGNOSIS OF metastatic sarcoma remains poor and overall survival rates at 2 years range from 20 to 40%. Tumour cells resist cytotoxic drugs by means of multiple mechanisms, and this resistance is thought to be a major cause of therapeutic failure. Multidrug resistance (MDR) due to an increased level of P-glycoprotein (Pgp) has been found in approximately 30% of human sarcomas [1]. Cyclosporin A (CsA) is able to block Pgp-related resistance *in vitro* and *in vivo* [2]. However, other mechanisms of resistance are also involved in sarcomas. We report on a woman presenting with a rapidly progressing metastatic leiomyosarcoma that expressed several resistance markers, detected by reverse transcriptase polymerase chain reaction (RT-PCR), and our attempt to reverse drug resistance by adding CsA to the chemotherapeutic regimen [3].

A 42-year-old Algerian woman was admitted to the Institut Curie Hospital in October, 1992, with the diagnosis of unknown primary leiomyosarcoma with breast and pulmonary metastases. Upon admission, she was jaundiced due to liver metastases. Insertion of a T tube resulted in a 3-week delay in the onset of chemotherapy during which bladder, skin and contralateral breast metastases appeared. A skin metastasis was biopsied before each cycle of chemotherapy and subjected to semi-quantitative RT-PCR, using β_2-microglobulin as the internal standard to determine the levels of Pgp, multidrug-related protein (MRP), topoisomerase IIα (Topo IIα) and gluthatione-S-transferase (GSTπ). Because of MDR1 mRNA overexpression at the time of diagnosis, we decided to give three cycles of vincristine, deticene, ifosfamide and doxorubicin associated with CsA (5 mg/kg loading dose followed by 15 mg/kg/day continuously infused for 48 h during doxorubicin infusion). A pharmacokinetic study of CsA levels (0, 15 and 20 h) was performed for each cycle and showed that an effective reversing level (mean > 2 μg/ml) could be obtained in the serum, mean 3.8 μg/ml (range, 2.4–5.1 μg/ml), while the CsA content in the skin metastasis (cutaneous punctures at 0, 15 and 20 h) was low, mean 30.5 ng/ml (range, 25–36 ng/ml). Despite three cycles of this treatment, her disease continued to progress.

Table 1. Drug-resistance markers detected by RT-PCR

mRNA	At diagnosis	Before second cycle	Before third cycle
MDR1	0.19*	0.32	0.43
MRP	0.022	0.018	0.022
Topo IIα	0.88	0.95	0.98
GST π	1.3	1.1	1.1

*Values represent the ratios of yield of the amplified target gene/yield of the amplified internal standard, β_2-microglobulin.

The addition of CsA to this chemotherapeutic regimen did not reverse the MDR phenotype (Table 1). Indeed, the MDR1 mRNA transcript continued to increase after two cycles (the ratio mdr1/β_2 was similar to that obtained for a 5-times doxorubicin resistant breast cell line, MCF7 taken as a reference). Despite a high serum CsA level, the tissue CsA level remained low, which could by itself explain the lack of effect on MDR. Before considering a 'reverser' as being ineffective, it must first be determined, as we did, that it enters the target cells. Furthermore, this inefficacy could also be due to the high level of GSTπ. However, the resistance of this rapidly progressing tumour cannot be attributed to the MRP gene, which encodes a 190-kDa membrane non-Pgp, that did not pass the threshold of positivity nor to the relative stability of the topo IIα-mRNA transcript [4]. The intrinsic and acquired multifactorial resistance of metastatic sarcoma may explain the inability to halt the progression of this patient's disease.

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Table 1. Length of hospitalisation for patients admitted with febrile neutropenia

	All patients (n = 35)	Discharge ANC < 500/μl (n = 12)	Discharge ANC ≥ 500/μl (n = 23)
Mean no. of days	4.7	4.1	5.1
Median no. of days	4	3	5
Range	2–17	2–9	2–17
≤ 5 days, n	25	10	15
≤ 7 days, n	31	11	20

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A Pilot Study of Early Hospital Discharge in Adult Patients With Fever and Neutropenia

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FEBRILE NEUTROPENIA is a common complication of cancer chemotherapy and an important contributor to the morbidity, mortality and cost of treatment. Whereas agreement exists regarding the principles that govern the initial management of the febrile neutropenic patient, there are little available data on which to base the decision of when to discontinue antibiotics and discharge from hospital those patients who become afebrile on antibiotics without an identified infection [1]. Several retrospective analyses have suggested that subsets of patients with fever and neutropenia can be identified for whom early discontinuation of parenteral antibiotics and hospital discharge may be safe and cost-saving [2–5]. We conducted a pilot study to prospectively test the feasibility of early hospital discharge of a low-risk subset of patients with chemotherapy-associated febrile nbeutropenia. Adults ≥ 18 years old receiving cyclic chemotherapy for solid tumours or lymphoma, and hospitalised with absolute neutrophil count (ANC) < 1000/μl and oral temperature ≥ 101°F, were eligible for immediate hospital discharge without antibiotics if they had an absolute neutrophil count (ANC) ≥ 100/μl and increasing, oral temperature < 99.5°F for at least 24 h and blood cultures obtained before antibiotic institution were sterile at 48 h incubation. Rehospitalisation was required for recurrent fever. These criteria differ from other recommendations in current practice in several ways. First, only the maturity of pre-antibiotic blood cultures required a delay in discharge, with additional cultures obtained during the hospitalisation not impacting upon discharge plans. Furthermore, in-hospital observation of patients after discontinuation of parenteral antibiotics was not required. Finally, attainment of a neutrophil count of 500/μl or 1000/μl was not required; a rising ANC was sufficient evidence of marrow recovery in the current trial.

35 patients, ages 21–68 years, were enrolled and eligible for early discharge. For these patients, median admission ANC was 196/μl (range 0–624/μl) and median ANC nadir was 70/μl (range 0–504/μl). Neutrophil counts at discharge and length of hospitalisations are shown in Table 1. One third of patients could be discharged with ANC < 500/μl. The median discharge ANC for all patients was 888/μl (range 100–56672/μl). The reasons for discharge of patients with ANC > 500/μl were persistant fever or active infection (14 patients), first eligible ANC was > 500/μl (4 patients), awaiting 48-h blood culture incubation (2 patients), and active serositis, failure to thrive, and pain control (1 patient each). Only 1 patient required rehospitalisation with recurrent fever but was *not* neutropenic at the time of readmission. 5 patients were discharged with oral antibiotics for identified infections, and colony-stimulating factors were used in 9 patients, at the discretion of treating physicians.

It is apparent that not every cancer patient with febrile neutropenia is at equal risk of infectious complications. This study shows that a population of febrile neutropenic adult patients may be identified early in their hospitalisation, and safely discharged without parenteral antibiotics. It was not possible in this pilot experience to determine the impact of oral antibiotics or myeloid growth factors on the management of these patients, and these are areas of active investigation. Our ability to modify the management of febrile neutropenic patients based upon risk stratification could measurably improve the care of patients, by reducing hospital days, the toxicity of parenteral medications, health care costs, and improving quality of life. Ongoing and planned multiinstitution trials are attempting to determine whether there is a benefit from the use of myeloid growth factors at the onset of febrile neutropenia [6–9], and whether outpatient parenteral antibiotic therapy is feasible for certain patients [10]. Each of these studies will further characterise the adult febrile neutropenic patient, and allow for individualised treatment based upon prospectively validated well-defined clinical characteristics.

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