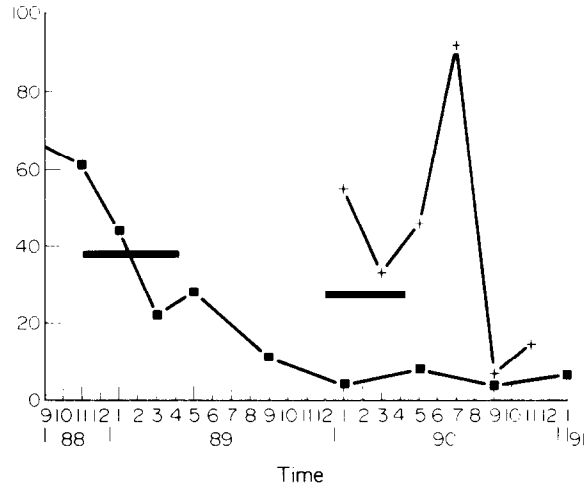

Fig. 1. Noradrenaline vs. time. Normal range < 5 μmol/l. —•— Patient 1, —|— patient 2, ▬ chemotherapy.

The serum noradrenaline levels (Fig. 1) declined slowly towards the second part of chemotherapy and normalised in February 1990, 10 months after treatment completion. Antihypertensives were discontinued in February 1990 and she remains asymptomatic. Her radiological abnormalities remain unchanged.

Patient 2, a 52-year-old man, presented with symptoms of episodic dizziness and had a left-sided intra-abdominal (extra-adrenal) phaeochromocytoma resected in 1987. His symptoms recurred in May 1988, when serum noradrenaline was rising. Treatment with atenolol and phenoxybenzamine provided symptomatic relief. In January 1990 his condition worsened with palpitations, 6 kg weight loss and poorly controlled hypertension. A repeat MIBG scan was again normal but computed tomography revealed intra-abdominal tumour recurrence and multiple skeletal metastases were shown on an isotope bone scan.

Chemotherapy (as for patient 1) was started and between February and June 1990, he received five cycles. Treatment was stopped when thrombocytopenia worsened with no change in tumour size. Following chemotherapy his noradrenaline decreased to 7 nmol/l and is now stable at 15 nmol/l (Fig. 1). His blood pressure remains controlled on atenolol; he is asymptomatic although the measurable tumour mass is unchanged.

Although the natural history for patients with these tumours is variable (with a 5-year survival of 44% [4]), improved pharmacological control of catecholamine secretion does not appear to influence mortality [5, 6]. Complete or partial biochemical responses were seen in nearly 80% of the 14 patients previously treated with this regime [7] (mean duration of response of 21 months) whilst only 8 had other evidence of tumour response (2 complete and 6 partial remissions). Treatment, however, was continued in this series until either disease progression or biochemical complete remission.

Both our patients had widely metastatic disease and the second had clear symptomatic deterioration associated with biochemical progression. Neither experienced the serious cardiovascular complications seen in patients with occult phaeochromocytoma who receive chemotherapy [8, 9]. There was a clear (delayed) fall in plasma noradrenaline associated with symptomatic improvement.

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Toxicity of Laevo-leucovorin and Dose-lowering

Federico Lonardi, Antonio Jirillo, Giorgio Bonciarelli, Giovanni Pavanato and Mario Balli

LEUCOVORIN IS widely used as a biomodulator in cancer chemotherapy. The D and L diastereoisomers have different metabolism and pharmacokinetics. L-leucovorin is the biologically active form and has recently become available. Therefore a 50% dosage reduction seemed a resonable step clinically, but the high level of toxicity we observed using L-leucovorin in otherwise well-tolerated schedules made such an approach questionable. Here we report our preliminary experience of 4 consecutive patients treated with L-leucovorin (Lederfolin, Lederle).

Two patients had advanced colorectal cancer and were scheduled for leucovorin as a 200 mg/m^2 push and 5-fluorouracil (5-FU) 400 mg/m^2 as a 15 min infusion on days 1–5 every 4

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weeks plus interferon-alpha-2b 3 × 10^6 U subcutaneously on alternating days (daily during 5-FU administration); 1 patient had metastatic etoposide-resistant gastric cancer (therapy as above, except for 5-FU at 370 mg/m^2 and no interferon).

L-Leucovorin was administered at 40–50% of the racemic leucovorin planned dose. All patients had grade III–IV mucositis immediately after induction that required supportive care and admission. Erythematous maculopapular rash (2 patients) with desquamation (one patient), diarrhoea grade III (1 patient), hair loss grade III (1 patient) and alopecia (1 patient) also occurred. In one colorectal cancer patient the L-leucovorin dose was lowered before starting the second cycle, but the same level of toxicity was observed; thus the drug was discontinued and toxicity in the third cycle became acceptable.

The fourth patient with advanced, heavily pretreated head and neck cancer, affected by dilatative cardiomyopathy with left ventricular intracavitary thrombosis, was scheduled for methotrexate 200 mg/m^2 every 3 weeks plus leucovorin 9 mg intramuscularly for 8 doses every 6 h starting 24 h after the methotrexate push. Chronic antithrombotic therapy (oral warfarin 2 mg daily) continued. Prothrombin time (INR, international normalised ratio) was monitored (value before chemotherapy 1.88). After three L-leucovorin injections, INR rose to 10, bleeding time was over 5 min and coagulation time over 2 h. Warfarin was immediately discontinued and 24 h later INR felt to 1.99. Vitamin K was administered.

We cannot be certain that L-leucovorin was responsible for such side-effects and pharmacological interactions, but the occurrence in 4 consecutive patients leads us to raise the possibility. Therefore further investigations are needed about the toxicity, dosage and schedule of L-leucovorin before wider clinical use. L-Leucovorin should be used at a lower dosage than 50% of the racemic schedules.

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Retrospective Analysis of 318 Cases of Uterine Sarcoma—Response

Peter Graham

READING THE report of Olah *et al.* [1] it would seem easy to conclude that radiotherapy has no role in the radical treatment of uterine sarcoma. They conclude that radiotherapy influences neither survival nor local control, except perhaps for mixed mesodermal tumours (MMTs).

When discussing survival Olah *et al.* concede that adjunctive radiotherapy was given on an ad-hoc basis without specific criteria and the trend for poorer survival in the complete resection plus radiotherapy group compared to the complete resection only group may reflect the selection of poorer prognosis patients for adjunctive radiotherapy. This possible bias might have been amenable to some assessment had the distribution of known prognostic factors (age, stage and histology) been tabulated for the different treatment groups. Similar logic should apply to the discussion of local recurrence, however, Olah *et al.* chose to ascribe the lack of improved local control with radiotherapy to the poor radiosensitivity of uterine sarcoma. This is despite their own evidence that adjunctive radiotherapy is associated with a 25% 5-year survival in patients with known residual disease compared to 0% 2-year survival without radiotherapy.

Olah *et al.* fail to state if the recurrence pattern was scored only by the site of first recurrence or overall recurrence. If the former method was used then the approximately 10% local recurrence rate may be falsely low. Salazar *et al.* demonstrated an overall pelvic recurrence rate of over 50% in the literature and the use of radiotherapy was associated with a halving of pelvic recurrence [2]. Accepting the morbidity of a 10% local recurrence rate compared to the possible toxicity of pelvic radiotherapy used in 100% may be reasonable but if the overall local recurrence rate (without radiotherapy) is higher, what level remains acceptable? Were there any prognostic factors which predicted for a higher rate of local recurrence? No discussion is given to whether there was evidence of a dose–response relationship despite the range of doses used. The average doses used appear to be low to moderate being mostly less than 50 Gy over an unspecified time and fractionation.

The majority of the study accrual period generally predated the widespread use of computed tomography as part of staging. The earlier detection of metastatic disease, especially lung metastases, with its resultant "stage creep" could potentially lower the distant: pelvic recurrence ratio and therefore increase the importance of local control. Furthermore, analysis at some sites has suggested local control may impact on survival [3, 4].

The one ray of radiotherapeutic hope offered by Olah *et al.* is for MMT. Tantalisingly, 3 long-term survivors following radiotherapy for stage III disease are cited, but although there were 25 stage III MMTs we do not know how many were treated by radiotherapy (alone?).

In conclusion, despite the size of this retrospective series I believe the real role of radiotherapy in uterine sarcoma remains to be defined and certainly cannot yet be dismissed. The need for controlled trials of adjunctive radiotherapy is at least as important as the need for similar trials of chemotherapy, especially given the generally negative trials for a survival benefit for adjuvant chemotherapy in adult soft tissue sarcomas and response rates for combination chemotherapy in uterine sarcoma generally in the region of only 20% [5, 6].

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