Table 1. Tumour localisations, symptoms, presenting therapy and outcome of 11 patients developing urothelial cancers after renal transplantation for end-stage analgesic nephropathy

Symptoms/findings at diagnosis (patients)		Localisation of urothelial cancer (patients)		Tumour stages at diagnosis* (patients)		Therapy (patients)		Outcome (patients)	
Haematuria	(5)	Bladder	(4)	pTa/pT1	(3)	Nephro-ureterectomy	(6)	DOD	(7)
Positive cytology	(4)	Renal pelvis	(4)	pT2	(5)	Transurethral resection	(3)	TRD	(1)
Positve ultrasound	(2)	Renal pelvis + bladder	(2)	pT3	(3)	Cystectomy	(2)	DEAD	(1)
Bone metastases	(1)	Renal pelvis + bladder + ureter	(1)					NED	(2)

DOD, dead of disease; TRD, therapy-related death; DEAD, death from non-tumour-related causes; NED, no evidence of disease; * Highest T-category per patient given in cases of multifocal disease.

The clinical outcome of therapy for urothelial cancer in patients with renal transplants is poor and from our 11 patients, 7 died from recurrent tumour after surgery, 1 from surgical-related complications and 1 from other causes. The median survival of 17 months is very short and may in part be explained by the fact that many tumours were detected at advanced stages due to their localisation in the upper urinary tract. Based on the high incidence, the predominant localisation in the upper urinary tract and the poor outcome of urothelial cancers after renal transplantation in patients with analgesic nephropathy, prophylactic bilateral nephro-ureterectomy should be prospectively evaluated after successful renal transplantation in this high risk group of patients. Currently, the prophylactic radical surgical removal of the possibly altered urothelium of the upper urinary tract and close follow-up of the urothelium of the bladder by routine cystoscopies might be the only approach that will have substantial impact on the long-term survival of patients with analgesic nephropathy who have received successful renal transplants.

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European Journal of Cancer Vol. 32A, No. 1, pp. 176–177, 1996.

Printed in Great Britain
0959–8049/96 $15.00 + 0.00

0959-8049(95)00466-1

Lonidamine plus Epirubicin and Cyclophosphamide in Advanced Breast Cancer. A Phase II Study

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LONIDAMINE, a dichlorinated derivative of indazole-3-carboxylic acid, belongs to a new class of anticancer agents with a unique mechanism of action. Initial *in vitro* studies suggested that lonidamine could affect the energy metabolism of cancer cells by inhibiting oxygen consumption and aerobic glycolysis [1]. Mitochondria have been found to be the primary intracellular target of this drug [2]. Clinical evaluation of lonidamine in different types of malignancies has been conducted in American and European institutions [3–7]. In our previous experience, we

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Revised 2 Aug. 1995; accepted 10 Aug. 1995.

found that clinically meaningful objective responses in patients with metastatic breast cancer could be achieved by administration of lonidamine as a single agent, although this activity was exceedingly modest in pretreated subjects [3]. Similar observations have been reported by other investigators [4]. In more recent laboratory studies, lonidamine has been shown to enhance the cytotoxicity of alkylating agents [8] and to reverse the resistance to anthracyclines in human breast cancer cell lines [9]. The drug resistance reversal properties of lonidamine seem promising in the treatment of patients with metastatic breast cancer [10]. The above considerations prompted us to test the addition of lonidamine to epirubicin and cyclophosphamide as a first-line therapy in a population of patients with advanced breast cancer. The present study evaluates this regimen with regard to toxicity and activity.

Eligibility criteria included histologically confirmed metastatic carcinoma of the breast, measurable progressive disease, ECOG performance status < 3, life expectancy > 6 months, WBC ≥ 4000/ml, platelets $> 150\,000$/ml and no prior chemotherapy for advanced disease. Informed consent was obtained from all patients. Treatment consisted of epirubicin 75 mg/m^2 and cyclophosphamide 600 mg/m^2 (EC) intravenously on day 1 every 21 days and lonidamine 600 mg/day orally continuously. A maximum of six courses was used unless there was evidence of disease progression or limiting (grade 4) toxicity. Patients were evaluated weekly for toxicity and every 3 weeks for response, as defined by WHO criteria. All patients treated on the protocol were registered and included in the overall response analysis. Of the 52 patients who entered the trial, 51 were assessable for toxicity (one patient died of cardiovascular disease not related to treatment or progressive disease). The patient characteristics are listed in Table 1. The median number of treatments with EC was six (range, 1–6), and the median received dose intensity (RDI) was 0.92 (range, 0.66–1.00). The combination of lonidamine plus EC was generally well tolerated. Some hair loss was seen in all the patients. 46 (90%) patients had nausea, including 16 (31%) patients who also had vomiting. 13 (25%) patients reported grade 1 mucositis. The incidence of severe myelotoxicity was very low, and only 2 (4%) patients experienced grade 4 leucopenia after receiving their first course of chemotherapy. Only 1 patient developed cardiotoxicity (grade 1). Lonidamine dosage was temporarily reduced in 4 patients (myalgia, 2 patients; asthenia, 1 patient; abdominal cramps, 1 patient).

There were 10 complete responses and 15 partial responses among the 52 patients, for a response rate of 48% (95% confidence limit, 35–62%). The median duration of remission for patients stable or better was 7.4 months (range, 2.2–19.0). Response rate according to dominant site of disease was soft tissue 79%, bone 36% and viscera 46%. No significant difference was found in objective response rate as related to prior adjuvant chemotherapy (received versus not received) and disease-free interval (< 1 year versus > 1 year). The objective response rate of patients receiving a RDI > 0.85 was significantly higher than that of patients receiving a RDI ≤ 0.85 (66% versus 27%; $P = 0.01$). It is of interest that, among 11 assessable patients with liver metastases, 5 (45%) achieved a complete response and 3 (27%) a partial response, for an overall response rate of 73%. Median RDI for these responding patients was 0.82 (range, 0.66–0.97).

In conclusion, lonidamine is an anticancer agent with a novel mechanism of action. Its clinical activity as a single agent in advanced breast cancer and other neoplasms is modest, while experimental evidence of animal tumours and tissue culture systems supports the hypothesis that lonidamine potentiates the antitumour effect of chemotherapy. This phase II study clearly shows that lonidamine +EC is active with acceptable toxicity. Whether lonidamine might improve the response rates of conventional chemotherapy remains to be investigated in future randomised trials.

Table 1. Patient characteristics (n = 52)

Total	52	
Median age in years (range)	56	(29–77)
Median disease-free interval in years (range)	2.4	(0–21)
Median ECOG performance status (range)	1	(0–3)
Menopausal status (%)		
Premenopause	11	(21)
Postmenopause	41	(79)
Previous adjuvant treatment (%)		
Endocrine therapy	15	(29)
Chemotherapy ± endocrine therapy	15	(29)
None	22	(42)
Previous treatment for metastatic disease (%)		
Endocrine therapy	12	(23)
None	40	(77)
Dominant site of disease (%)		
Soft tissue	14	(27)
Bone	14	(27)
Visceral	24	(46)
No. of disease sites (%)		
1	27	(52)
2	15	(29)
≥ 3	10	(19)

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