importance to the patients [2]. A choice between treatments offering different chances of long-term survival and different levels of toxicity could also be made by combining them into an overall index, but it might be more helpful to have a decision rule. "A is preferred to B, if long term survival is increased by more than x% *as long as* toxicity is not increased by more than y%" [2].

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Clinical Study and Pharmacokinetics of Lonidamine in Advanced Non-Small Cell Lung Cancer

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THERE IS an urgent need for more effective medical treatment against non-small cell lung cancer (NSCLC). Platinum-containing chemotherapy regimens have produced response rates of 30–40% in patients with advanced NSCLC [1, 2] but the duration of response is short and survival benefit debatable [3, 4]. Against this background the use of new agents in phase II trials is reasonable and allows a better evaluation of a new drug. Lonidamine is a substituted indazole carboxylic acid derivative which induced mitochondrial damage and inhibited anaerobic glycolysis *in vitro* [5] and has shown phase I/II antitumour activity [6–8].

We evaluated lonidamine in 10 patients with advanced NSCLC, none of whom had received chemotherapy. The median age was 55 (range 34–66) years, and there were 7 male and 3 female patients, all with performance status WHO grade 0 or 1. Lonidamine was started at 75 mg three times a day, increasing over 7 days to 600 mg daily in divided doses and then reducing to 400 mg daily in divided doses in those patients experiencing unpleasant toxicity at higher doses.

No objective responses were seen. 1 patient had a minor regression of a pleural effusion. Median duration of treatment was 74 (range 31–146) days and treatment was discontinued because of non-haematological toxicity (myalgia, testicular pain) in 4 patients and progressive disease in 6 patients. No haematological or metabolic toxicity was seen. Details of toxicity are in Table 1. Pharmacokinetic studies were conducted over a 24 h period in 8 patients after 28 days at 600 mg daily in divided doses. Lonidamine levels were measured by reverse HPLC with fluorescence detection. The mean (S.D.) peak and trough plasma levels were 10.8 (4.0) μg/ml and 3.2 (2.2) μg/ml respectively. The time to peak lonidamine concentration was 1.6 (1.0) h and the half-life 4.7 (3.3) h.

Table 1. *Toxicity (worst recorded grade)*

Grade	0	1 (mild)	2 (moderate)	3 (severe)
Myalgia	2	4	3	1
Testicular tenderness (7 patients)	3	3	1	0
Indigestion	0	2	0	0
Hallucinations	0	0	1	0
Venous thrombosis	0	0	1	0
Joint aches	0	0	1	0

Our failure to detect any response in 10 patients, despite achieving plasma levels through a 24 h period, indicates that there is less than a 5% chance of lonidamine having a true response rate of 30% [9] and this study was therefore discontinued. In previous studies a partial response rate of only 10% has been reported in 69 patients with NSCLC [7, 8] and in 20 patients with SCLC [8]. In addition the side-effects observed in our study, especially myalgia (80%) and testicular pain (57%), which were similar to those previously reported [7, 8] were considered unacceptable in a palliative context. This study confirms the lack of activity of lonidamine as a single agent in NSCLC and although combination therapy of lonidamine with cytotoxic drugs or radiotherapy is under exploration, toxicity may limit the application of lonidamine unless it is used at lower doses.

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