immunoreaction for A1AT and human chorionic gonadotropin. The ultrastructural examination showed the presence of closely apposed polygonal cells containing intercellular canaliculi characterised by a lot of delicate microvilli and intercellular junctions consistent with hepatoid differentiation (Fig. 1).

The final diagnosis was YST with areas of hepatoid differentiation.

In the female genital tract YST is most frequently encountered in the ovary [4, 5]. It is exceedingly rare in the vulva [2, 3 ,6]. The cases of YST of the vagina or uterine cervix bring the total number of reports in the world literature to approximately 50.

Microscopically the YST has more than one histopathological pattern: festoon, reticular, solid and polyvescicular. A peculiar variant of YST with hepatoid differentiation has been described in the ovary [7]. The clinical presentation of the vaginal YST must prompt us to differentiate it from botryoid sarcoma; the diagnosis is evident on histological examination.

Differential diagnosis must be also made with clear cell carcinoma. In YST diagnosis must be based upon the absence of hobnail pattern, the presence of Schiller–Duval bodies and the various histological patterns characteristic of YST and the immunohistochemical demonstration of AFP.

In the adult YST with an predominantly hepatoid pattern differential diagnosis must be made with a metastasis of hepatocellular carcinoma [7]. However, the clinical examination showing the presence of areas with typical YST patterns aid in the diagnosis.

The prognosis for these tumours with modern chemotherapy without radiation therapy or ablative surgery is very good.

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Eur J Cancer, Vol. 27, No. 4, pp. 518–519, 1991.
Printed in Great Britain
0277–5379/91 $3.00 + 0.00

Study Design in Evaluation of Combined Modality Treatment

Denise Howel and Margaret Jones

THE RECENT paper by Yarnold *et al.* [1] highlighted the problems of evaluating treatments with many criteria of interest (e.g. toxicity, local control and survival). Whilst agreeing that there are real problems, we would disagree with the solution proposed by these authors.

It is useful to classify a proposed trial by the system described by Schwartz *et al.* [2] i.e. as "explanatory" or "pragmatic". An explanatory trial is aimed at increasing our understanding of the mechanism of combined therapy by addressing a question such as "Does the addition of chemotherapy to radiotherapy change the biological effect, compared to radiotherapy alone?" whereas a pragmatic trial would aim to answer a question like "What combination of radiotherapy and chemotherapy gives the best therapeutic effect?" The choices of dose levels, assessment criteria and suitable subjects cannot be simultaneously appropriate for both research questions, so a decision must be made early between the two approaches.

If a two-arm explanatory trial were planned with n subjects per arm, then subjects would receive radiotherapy or the combined therapy with the same radiation dose so that any difference could be attributed to chemotherapy itself. A suitable primary assessment criterion would be biologically meaningful (e.g. local control rather than survival, since survival is affected by factors other than treatment) with toxicity as a secondary criterion. It would be possible to carry out a four-arm trial (a 2×2 factorial experiment) to investigate the possible interactive effects (positive and negative) of radiotherapy and chemotherapy with similar subject numbers to a two-arm trial. If the four combinations of two levels of radiotherapy (low/high) and two levels of chemotherapy (present/absent) were used on $n/2$ subjects each, the single and joint effects of the two modes of treatment could be obtained in one trial.

However, a factorial design is only suitable for an explanatory trial and not for a pragmatic trial [2]. To facilitate the attribution of any extra effects to chemotherapy alone, the protocols should be strictly adhered to and all other factors should be equalised. This strategy and the choice of dose levels may lead to ethical problems with human subjects in explanatory trials once the side-effects are established.

In a pragmatic trial, interest centres more on therapeutic benefit than on biological effect, so assessment criteria are likely to include long-term survival and toxicity measures as opposed to local control. Treatment combinations would be chosen to provide an acceptable level of toxicity, which might mean chemotherapy in combination with a lower radiotherapy dose than usual. The choice of the lower dose is difficult and Yarnold *et al.* discount this option, since the wrong adjustment might be made. However their suggestion of a third arm to the trial with an increased radiotherapy dose has the same problem.

Using the distinction between explanatory and pragmatic trials it can be seen that the three-arm solution proposed by Yarnold *et al.* has some of the disadvantages of explanatory trials, since the extra treatment is not one which would be given in practice, but is not sufficiently tightly controlled to claim the advantage of being able to attribute any differences to chemotherapy itself. There are very real difficulties in deciding between treatments if more than one criterion is necessary. It is possible that assessments of the various forms of toxicity could be combined into an overall index, either taking the correlations between assessments into account [3] or using their relative

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Received 15 Jan. 1991; accepted 22 Jan. 1991.

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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Eur J Cancer, Vol. 27, No. 4, p. 519, 1991.
Printed in Great Britain
0277–5379/91 $3.00 + 0.00

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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Received 11 Jan. 1991; accepted 25 Jan. 1991.

Acknowledgements—We would like to thank Angelini Pharmaceuticals ACRAF (UK) Ltd who sponsored this work and Julia Holborn for preparation of this manuscript.