Paper

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Leo 1031 (NSC-134087) in Gynecologic Malignancies

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Key Words

Leo 1031
Chemotherapy
Ovarian carcinoma
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Abstract

Thirty-nine patients with gynecological malignancies who had failed on conventional chemotherapeutic agents were treated with Leo 1031 to study the effective dosage and toxicity of the compound in gynecological malignancies. Six patients with ovarian adenocarcinoma were also treated subsequently by using this compound as primary therapy. Comparable results (33% response rate) were obtained with excellent subjective response and minimal hematologic toxicity. Leo 1031 given 30 mg per day was well tolerated by most of the patients but increasing the dose to 40 mg per day led to development of severe hematologic toxicity with no change in response rate. No patients developed clinical evidence of steroid toxicity.

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Introduction

LEO 1031 (Prednimustine, Stereocyt) is a chlorambucil ester of prednisolone. It has been found to be effective in a variety of animal tumors [6] including L1210 and Walker 256 carcinoma. These responses occur with a much higher therapeutic index than was observed with either BCNU or cyclophosphamide [3]. This was a result of the low bone marrow stem cell toxicity of the drug. It is postulated that the steroid would act as a carrier for the alkylating agent to cross cell membrane and past work seems to indicate that the lipophilic ester of alkylating agents might remain intact for sufficient length of time to carry the alkylating agent into previous sanctuary areas.

Because of the effectiveness of chlorambucil in ovarian adenocarcinoma [J] LEO 1031 was evaluated (Phase I and II study) in women with advanced ovarian adenocarcinoma not amenable to further surgery or radiation therapy. In addition, 10 patients with other gynecologic malignancies were treated with LEO 1031, after progression on other chemotherapeutic agents.

Material and Methods

From June 1975 to June 1977, 45 patients with histologically documented advanced gynecological malignancies were entered into the Phase I and II study. The study was carried out to determine the effective dosage of this compound in gynecological malignancies. The dosage used was determined utilising the experience of previous Phase I and II studies in lymphocytic lymphoma and chronic lymphocytic leukemia studies, and also use of this compound in other malignancies [4,2],

LEO 1031 was initiated at a dose of 20 mg orally daily, and if tolerated the dose was increased to 30 mg daily. Each 20 mg LEO 1031 tablet contains 8.6 mg of chlorambucil and 11.4 mg of prednisolone as per calculations based on molecular weights. Six patients had their dose increased to 40 mg per day to evaluate if increasing the dose increased the therapeutic response. Patients remained on 30 mg per day if the platelet count was greater than 100,000/mm³ or white count greater than 3000/mm³. Complete blood counts were obtained weekly.

Definition of Tumor Response

Complete response was defined as complete disappearance of all measurable disease. Partial response was defined as greater than 50 % reduction in tumor mass or the complete control of malignant effusions. Stationary disease was defined as the absence of growth of measurable disease, or change in the malignant effusions. Progression was defined as a 25 % or more increase in measurable disease, an increase in malignant effusion, or appearance of a new lesion. All of the above response criteria must have been present for a period of one month or more.

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LEO 1031

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Results

Response

Therapeutic response — Therapy in recurrent ovarian adenocarcinoma. Two of the 17 (12 %) evaluable patients achieved a partial response, with response lasting 2 and 4 months respectively. Both of these patients had an adequate trial with alkylating agents in the past and had failed. One of these patients received melphalan for 2 courses and 2 courses of 5FU plus melphalan and had progression of disease. The other patient had received multiple courses of 5FU with melphalan,

high dose methotrexate and Cytosan and hexamethylmelamine, methotrexate, 5FU and Cytosan chemotherapy with progression of the disease. There were no complete responders.

Primary therapy and ovarian adenocarcinoma. Two of the six patients (33 %) treated primarily had partial responses lasting 7 and 15 months, with the latter patients still responding. Two patients had stationary disease for 2 months and 2 patients progressed. There were no complete responders. Of the 23 patients with ovarian adenocarcinoma, there were 4 (17.3 %) partial responders.

Therapy in endometrial carcinoma. – Four patients received LEO 1031 after progressing on progesterone therapy. There were no responders in this group. Two patients had stationary disease lasting 2 and 5 months respectively, and 2 patients progressed.

Other gynecologic malignancies. One patient with uterine sarcoma, who had failed on multiple chemotherapeutic agents, had a partial response lasting 11 months. Two patients with recurrent cervical cancer did not respond. One had stationary disease for 6 months while the other patient progressed. One patient with carcinoma of the fallopian tube continued to have stationary disease for 7 months. One patient with clear cell carcinoma of the vagina had stationary disease for 2 months, but did not return for further therapy.

Subjective response. Eighteen patients felt subjectively better. Fourteen patients had no subjective improvement.

Toxicity. Twenty-six of the 32 patients (81%) receiving 30 mg per day had no hematologic toxicity (white blood count $\geq 3000/\text{mm}^3$ or platelet count $\geq 100,000/\text{mm}^3$). Five patients developed leukopenia ($1500\text{--}2500/\text{mm}^3$), but tolerated reduction to 20 mg per day without leukopenia. One patient's leukopenia persisted and she could not be re-treated. Four of the 32 patients developed thrombocytopenia ($50,000\text{--}99,000/\text{mm}^3$) which reverted to normal at 20 mg per day of LEO 1031. Three of these four patients also had concomitant leukopenia.

Five of the 6 patients receiving 40 mg per day could not tolerate this dose because of leukopenia and thrombocytopenia. One patient died 2 weeks after starting therapy from progressive disease. No patients developed clinical evidence of steroid toxicity. One patient developed herpetic rash while on therapy.

Discussion

LEO 1031 at a dose of 30 mg per day was well tolerated hematologically in 81% of 32 evaluable patients. Five of the 6 remaining patients could tolerate a reduction in dose to 20 mg per day.

Of the 23 patients with ovarian adenocarcinoma only 17.3 % responded, all of whom were partial responders. This included a 12 % partial response in 17 patients receiving LEO 1031 as third line therapy, and 33 % (2/6) receiving it as primary therapy. Only 1 of 9 patients with other gynecologic malignancies responded, i.e. a partial response in a patient with recurrent uterine sarcoma.

Over 50% (18/32) of the patients on this therapy had subjective improvement while on therapy. The use of steroid structure as carrier for alkylating agents, thus increasing the specificity and decreasing the toxicity, has been proposed by Konyves and Liljekvist [5]. The subjective response could partly be explained from the above theory with decreased toxicity from alkylating agents with a steroid molecule and partly due to steroid itself.

The use of this drug as primary therapy in 6 patients with ovarian adenocarcinoma showed a 33 % response rate (2/6) and 33 % (2/6) had stationary disease. This response rate is comparable if

not better with other single agent alkylating agents used in treatment of ovarian carcinoma [1,7]. Although the response rate was low in this study, we intend to study steroid receptor sites in ovarian and uterine malignancies to further utilise similar compounds in the future.

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