Clinical Trial Results Disclosure Synopsis

Name of Sponsor: Ciba-Geigy Corporation
556 Morris Avenue
Summit, NJ 07901

Title of Study: Phase II Trial of Liposomal MTP-PE in Combination with Chemotherapy for Treatment of Patients with Osteosarcoma who have Failed Prior Adjuvant Therapy

Phase of Development: Phase 2

Name of Active Ingredient: N-acetyl muramyl-L-alanyl-D-isoglutaminyl-L-alanine-2-(1,2-dipalmitoyl-Sn-glycero-3-) (hydroxyphosphoryl-oxy)] ethylamide monosodium salt (MTP-PE)

Name of Finished Product: Liposomal MTP-PE intravenous infusion

Investigator: Three principal investigators enrolled subjects in the study.

Study Site: Subjects were enrolled at three sites in the United States.

Publication Based on the Study at Time of Study Completion: None

Study Period:

Date first subject signed informed consent form: 04 December 1991
Date of last subject’s last visit/contact (from the Clinical database): 09 October 1992

Objectives:

1. To evaluate the safety and tolerability between liposomal MTP-PE and ifosfamide and between liposomal MTP-PE and cisplatin in patients with osteosarcoma who have relapsed during or following previous adjuvant chemotherapy.

2. To evaluate histologic and pathologic patterns in tumor tissue resected following treatment with liposomal MTP-PE in combination with ifosfamide or cisplatin.

3. To determine, when possible, the interaction between liposomal MTP-PE and ifosfamide and between liposomal MTP-PE and cisplatin on selected parameters of immunomodulatory activity and organ functions.

4. To assess disease free interval and survival of patients treated with liposomal MTP-PE combined with ifosfamide or cisplatin.

Methodology:

This was a prospective open-label, multicenter, non-randomized trial in patients with osteosarcoma who have developed recurrent disease during or following previous chemotherapy. Subjects received intravenous (IV) administration of liposomal MTP-PE (twice weekly for 12
weeks, then once weekly for an additional 12 weeks) along with the appropriate concurrent chemotherapy regimen determined by their prior medical history: either cisplatin (6 cycles at 28 day intervals) or ifosfamide (8 cycles at 21 day intervals).

Patients were followed for a minimum of 1 year post liposomal MTP-PE treatment to assess disease status, and when possible until relapse or death.

**Number of Subjects:**
Planned: 15 subjects
Enrolled: 12 subjects
Safety Analysis Set: 12 subjects

**Diagnosis and Main Criteria for Inclusion:**
Subjects were males and non-nursing females using acceptable contraception, between the ages of 8 and 70, with a performance status on the Zubrod Scale less than 2, who provided informed consent indicating that the patient and/or guardian is aware of the investigational nature of the treatment.

They must have histologically proven osteosarcoma and have a prior history of developing resectable metastases during or after adjuvant chemotherapy following primary tumor resection, or have resectable metastases that persist despite chemotherapy. Patients entering this trial must either demonstrate no evidence of disease or have measurable disease which is resectable, and be candidates for chemotherapy with cisplatin or ifosfamide. They must have adequate blood counts and preserved coagulation, renal and hepatic functions

**Duration of Treatment:** 24 weeks

**Test Product, Dose and Mode of Administration, and Lot Number:**

<table>
<thead>
<tr>
<th>Study Medication</th>
<th>Product Dose Strength and Form</th>
<th>Study Dosage</th>
<th>Mode of Administration</th>
<th>Drug Product Lot Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomal MTP-PE</td>
<td>2 mg/m² in 50 mL buffered solution</td>
<td>2 mg/m²</td>
<td>IV infusion</td>
<td>15/473/1</td>
</tr>
</tbody>
</table>

**Reference Therapy, Dose and Mode of Administration, and Lot Number:**
Not applicable
Criteria for Evaluation:

- Tumor response
- Disease-free interval
- Safety and tolerability

Statistical Methods:

Data will be tabulated with summary statistics with respect to the following:

1. Demographic and baseline characteristics.
2. Safety observations and measurements.
3. Efficacy observations and measurements

SUMMARY OF RESULTS:

Baseline Demographics and Other Relevant Characteristics:

Of twelve patients enrolled in the trial, the mean age was 16 years (range from 9-21), 8 were male and 4 were female; 9 were white, 1 black, 1 oriental, and 1 was classified as other; 7 had no evidence of disease (NED) at baseline, while 5 had measurable disease; and 9 had normal activity levels, 1 was fully ambulatory and 2 were in bed less than 50% of the time.

Seven patients (58%) reported significant past medical history or concomitant diagnosis and 8 (66.6%) reported concomitant medications/therapies at Visit 1. All of the patients had previous chemotherapy and cancer-related surgeries, two patients had previous radiation therapy, and one patient had previous immunotherapy. Nine patients had symptoms relating to malignancy or concomitant therapy present at Visit 1.

Subject Disposition:

The initial intent was to enroll a total of fifteen patients at three study sites; however, after a total of twelve patients had been enrolled, the Children's Cancer Study Group investigators felt that the data were sufficient to support the initiation of the Phase III National Cancer Institute study of adjuvant therapy using a combination of liposomal MTP-PE and chemotherapy, and the study was closed to enrollment.

Of the twelve patients enrolled into the trial, nine were treated with liposomal MTP-PE and ifosfamide and three were treated with liposomal MTP-PE and cisplatin, but one patient developed ototoxicity secondary to cisplatin and was switched to ifosfamide. Two patients completed the trial, ten were discontinued prematurely and all are included in the safety summary.
Efficacy Results:
Only safety and tolerability were analyzed for this trial. During the conduct of the trial, it became evident that it was not possible at the various sites to collect material for histologic and pathologic assessment in tumor tissue nor was it feasible to collect serum samples for assessment of parameters of immunomodulatory activity.

Safety Results:
The majority of patients had no significant change in Zubrod Performance Status from their baseline evaluations, but two patients declined from normal activity to 100% bed ridden, including Patient 103 and another who had developed progressive disease.

Most of the more common adverse experiences such as fatigue, fever, rigors, and tachycardia were attributed to liposomal MTP-PE, as was exacerbation of pre-existing asthmatic bronchitis in two patients.

Considered by the investigators as unrelated to liposomal MTP-PE administration and more likely attributable to the concomitant chemotherapy were the most commonly seen serious adverse experiences of hematologic toxicities including leukopenia, neutropenia, granulocytopenia, thrombocytopenia, and anemia; as well as nausea and vomiting recorded from 40 to 70 percent overall.

Two patients were prematurely discontinued from the trial due to adverse experiences and/or laboratory abnormalities. Two patients had pericardial and pleural effusions, only one of which was considered to have probable relationship to liposomal MTP-PE administration. One patient experienced a worsening of hypokalemia and hypomagnesemia that were present at Visit 1; two patients had Grade 3 rigors, one patient with diagnosis of asthma at visit 1 had wheezing; one patient had itching; two patients had hypotension; two patients had vomiting; two patients developed bacterial infections; one patient developed ototoxicity secondary to cisplatin; one patient developed a thrombus of the right atrium associated with an indwelling catheter. This patient was treated with urokinase and subsequently developed fever, chills, and tachycardia secondary to urokinase administration.

No deaths occurred while patients were participating in the trial. However, two patients died shortly following the trial because of tumor-related progressive disease.

Study ID Number:
PROTOCOL # 10

Other Study ID Number(s):
UTN: U1111-1144-5763
TIP #914042

DATE OF SYNOPSIS: 15 July 1994

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