

Muramyl Tripeptide-Phosphatidyl Ethanolamine Encapsulated in Liposomes (L-MTP-PE) in the Treatment of Osteosarcoma

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Abstract Bacille Calmette-Guerin (BCG) has been used for decades as an immune stimulant to treat cancer. Early work by Fidler and Kleinerman identified muramyl dipeptide (MDP) as a critical component of the BCG cell wall which retained most of the immunostimulatory properties of the native BCG. Addition of a peptide to MDP resulted in muramyl tripeptide (MTP) which allowed incorporation into liposomal membranes. The resulting pharmaceutical, liposomal muramyl tripeptide phosphatidyl ethanolamine (L-MTP-PE or mifamurtide) showed activity in preclinical models of human cancers. Phase I studies documented the safety of the compound for human administration. These trials did not reach a maximally tolerated dose (MTD), and the dose chosen for phase II trials was a biologically optimized dose, not an MTD. Phase II studies showed decreased risk of further recurrence in patients who received mifamurtide after surgical ablation of metastatic osteosarcoma. A phase III prospective randomized trial demonstrated a statistically significant reduction in the risk of death from osteosarcoma when MTP was added to systemic chemotherapy for the treatment of localized osteosarcoma. The same trial allowed treatment of patients who presented with initially metastatic disease. While the overall and event-free survival was improved in patients with metastatic osteosarcoma who received L-MTP-PE, the sample size was small and the improvement did not achieve conventional statistical significance. From 2008 to 2012, patients with metastatic and recurrent osteosarcoma were given L-MTP-PE in an expanded access trial, and the results suggest a decreased risk of subsequent recurrence and death with the inclusion of L-MTP-PE in the treatment strategy for these high-risk patients.

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Introduction

The concept of using immunotherapy to treat chemotherapy-resistant tumors has been around for several decades. The use of T-cells, lymphokine-activated killer cells, interferon, and NK cells have been explored for the treatment of solid tumors including melanoma, brain tumors, hepatoblastoma, and lymphoma. While there have been reported successes particularly in the use of α -interferon (α -IFN) to treat metastatic melanoma, improvement in survival for large numbers of patients with other solid tumors has been modest. Furthermore, there is no standard of care treatment that combines cytokines, T-cells, or NK cells with chemotherapy for newly diagnosed patients.

The one immune cell that has largely been ignored in terms of its potential in cancer treatment is the macrophage. In this chapter, the history and development of the macrophage-activating agent, L-MTP-PE, will be traced from the first concept through preclinical studies, phase I, phase II, and phase III trials. The phase III trial demonstrated for the first time that an agent that targets and activates macrophages can be successfully combined with chemotherapy to achieve an improvement in long-term outcome as measured by a significant decrease in the mortality rate at 6–8 years. The use of L-MTP-PE together with chemotherapy in newly diagnosed nonmetastatic osteosarcoma patients resulted in a decrease in the death rate as well as an improvement in both the progression-free and long-term survival of patients with this disease. Targeting the macrophage and activating its tumoricidal function is therefore an approach that warrants more focus and additional clinical investigations.

Background

Bacille Calmette-Guerin (BCG) was isolated after hundreds of passages to create a vaccine against tuberculosis. As early as the 1930s, BCG was used to stimulate the immune system in patients with cancer in hopes that their enhanced immunity would lead to regression of cancer. BCG remains in use to the present as an adjuvant for superficial bladder cancer. Injection of BCG into superficial bladder cancers leads to tumor regression [1].

Zwilling and Campolito demonstrated that BCG could activate alveolar macrophages to become tumoricidal to autologous tumor cells [2]. Japanese investigators localized this macrophage-activating activity to the cell-wall skeleton [3]. A synthetic peptidoglycan, *N*-acetyl muramyl-L-alanine-D-isoglutamine, or muramyl dipeptide (MDP) was formulated to correspond to a component found in a water-soluble extract of cell wall of mycobacteria [4]. Benacerraf and colleagues demonstrated that MDP could serve as an adjuvant to enhance immune responses [5]. Fidler and colleagues demonstrated that encapsulating lymphokines in liposomes resulted in more efficient activation of macrophages [6]. The same group showed that liposome-encapsulated MDP could result in activation of tumoricidal properties in rat alveolar

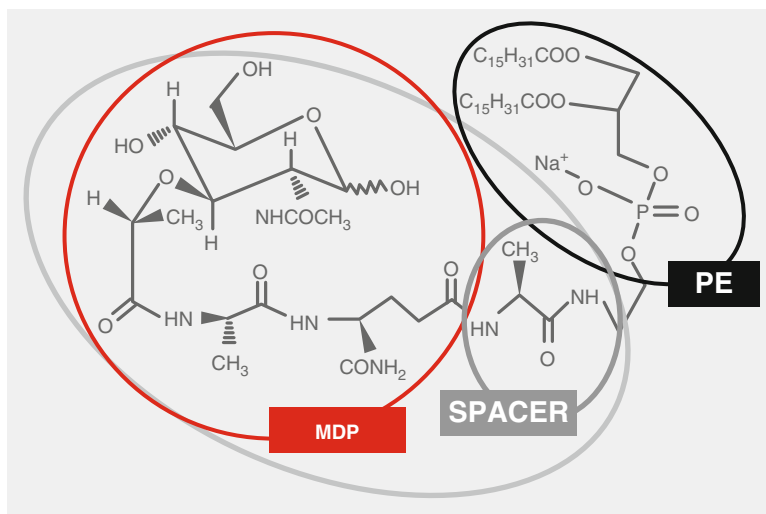


Fig. 1 Muramyl dipeptide (MDP) is the component of the BCG cell wall which retains the immune-stimulating properties of BCG. MTP-PE was created by adding a peptide spacer and binding the resulting tripeptide to phosphatidyl ethanolamine to improve lipid solubility. Copyright of the image is held by Paul Meyers. Used with permission from Paul Meyers

macrophages [7]. It was shown that unmodified MDP was eliminated from the systemic circulation very rapidly [8]. Fidler and colleagues demonstrated that intravenous injection of liposomes containing MDP could eradicate spontaneous metastases and activate alveolar macrophages in a murine model [9].

It was shown that low-molecular-weight compounds such as MDP could leak from liposomes. Fidler's group demonstrated that modification of MDP by the addition of a third peptide to create muramyl tripeptide (MTP) followed by incorporation into multi-lamellar liposomes enhanced macrophage activation [10] (Figs. 1 and 2). Kleinerman and Fidler initiated work using liposome-encapsulated muramyl tripeptide (L-MTP-PE) in human cells [11]. They demonstrated that human blood monocytes could be rendered tumoricidal after activation with L-MTP-PE.

Early Clinical Investigation

The first studies of L-MTP-PE in humans were performed at the MD Anderson Cancer Center (MDACC). The results of the first phase 1 trials were reported in 1989 [12]. Toxicity was moderate, with the most common side effects reported including chills, fever, malaise, and nausea. The maximum tolerated dose (MTD) was reported to be 6 mg/m². Imaging studies of radiolabeled L-MTP-PE showed rapid uptake in the spleen, liver, lungs, nasopharynx, and, in two patients, tumor.

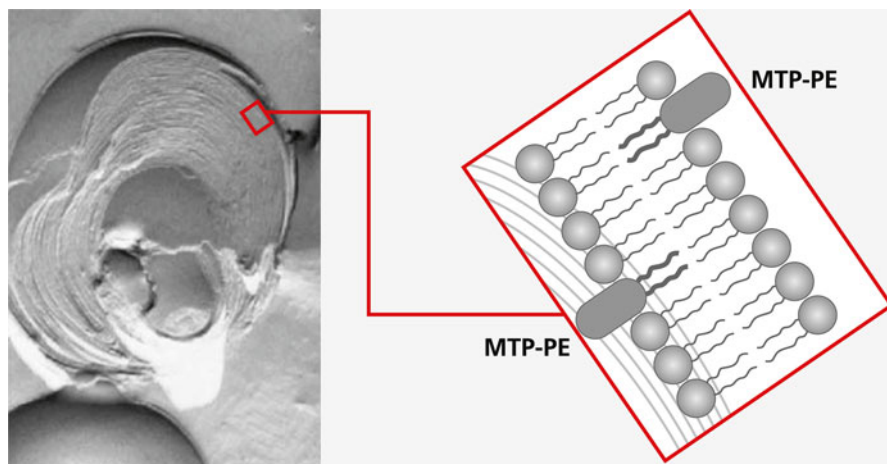


Fig. 2 When muramyl tripeptide-phosphatidyl ethanolamine is incorporated into liposomes, the compound intercalates into the membrane bilayers of the liposome to create the pharmaceutical L-MTP-PE. Copyright of the image is held by Paul Meyers. Used with permission from Paul Meyers

Kleinerman reported the tumoricidal properties of peripheral blood monocytes from the patients who were the subjects of that phase I study [13]. She reported that activation of monocyte-mediated tumoricidal activity was found in 24 of 28 patients at some point during therapy. While the MTD for the clinical trial was reported to be 4–6 mg/m², the optimal biological dose for macrophage activation was 0.5–2.0 mg/m². This concept that optimal biological dose may be lower than MTD has been confirmed in many studies of biological agents for the treatment of cancer [14].

L-MTP-PE had been shown to be capable of inducing lung-resident alveolar macrophages to become tumoricidal. It had been shown to prevent tumor cells from developing into pulmonary metastases in murine models. These observations suggested that L-MTP-PE might be useful in preventing the progression of microscopic metastases in the lung to clinically detectable size, making L-MTP-PE particularly interesting in osteosarcoma. At initial presentation, most patients with osteosarcoma do not have clinically detectable metastatic disease. In the absence of systemic therapy, 90 % of these patients will go on to develop clinical metastases, and the great majority of these metastases will appear first in the lung [15]. This makes osteosarcoma a good candidate disease in which to study an agent which activates pulmonary macrophages to become tumoricidal.

Many studies of new anticancer drugs are performed in models in which human tumor cell lines are grown in immunodeficient mice. These heterotopic xenografts are an imperfect model because human tumor cell lines are often significantly mutated from the tumor of origin, tumors grow in compartments which are different from the compartments in which they spontaneously arise, and the lack of an immune system makes it impossible to test therapies that incorporate host immune responses. Dogs develop osteosarcoma spontaneously. Osteosarcoma in dogs arises

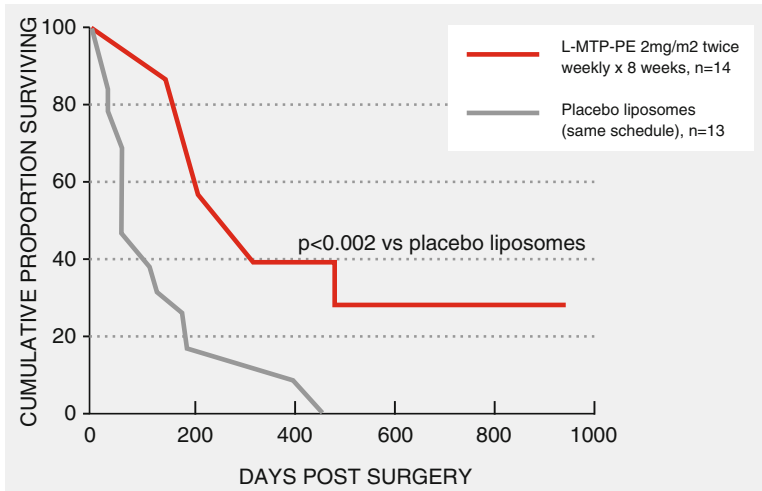


Fig. 3 MacEwen et al. conducted a prospective randomized double-blind study of L-MTP-PE as adjuvant therapy in dogs with osteosarcoma following amputation of the extremity with the primary tumor. Adjuvant L-MTP-PE resulted in a statistically significant improvement in the overall survival and the apparent cure of some animals. Copyright of the image is held by Paul Meyers. Used with permission from Paul Meyers

in the long bones and metastasizes to the lungs, recapitulating human disease. Osteosarcoma in dogs is an excellent natural model in which to study new agents for the treatment of human osteosarcoma.

MacEwen and colleagues conducted a double-blinded placebo-controlled trial of L-MTP-PE in dogs with osteosarcoma [16]. All the dogs had osteosarcoma without clinically detectable metastatic disease. All dogs underwent amputation of the tumor-bearing limb. Dogs were randomly assigned to receive L-MTP-PE or a placebo consisting of empty liposomes. Historic data suggested that all dogs with osteosarcoma treated with amputation alone would rapidly develop metastatic disease and die. The prospective randomized study confirmed the historical experience. All of the dogs assigned to receive placebo developed metastasis, and the median survival time was 77 days. Median survival for the dogs treated with L-MTP-PE was 222 days, a statistically significant improvement, and 4 of 14 treated dogs remained free of recurrent osteosarcoma 1 year following amputation (Fig. 3). These encouraging results supported the conduct of subsequent phase II trials in human patients and ultimately the randomized phase III trial.

Investigators at the MDACC conducted a phase II study of L-MTP-PE in patients with osteosarcoma which had recurred with pulmonary metastases after initial therapy with surgery and combination cytotoxic chemotherapy [17]. All patients were rendered disease free by surgical resection of pulmonary metastases. L-MTP-PE was administered twice weekly for 12 weeks (group 1). An additional cohort of patients received L-MTP-PE twice weekly for 12 weeks and then once weekly for an additional 12 weeks for a total of 24 weeks of treatment (group 2).

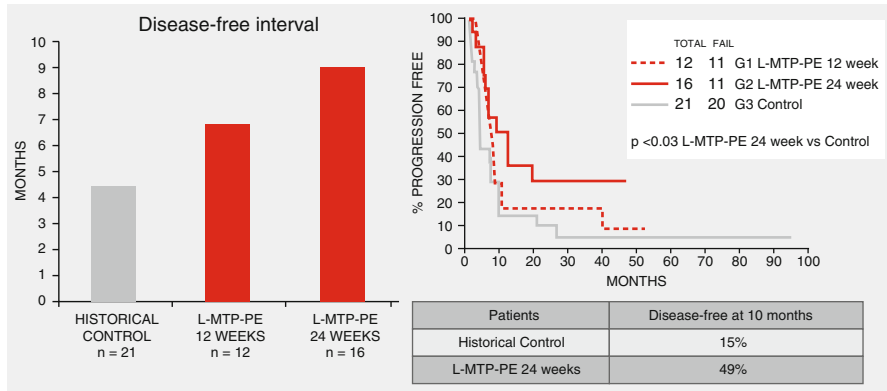


Fig. 4 Investigators at the MD Anderson Cancer Center performed a phase 2 trial of adjuvant L-MTP-PE in patients with metastatic recurrent osteosarcoma whose pulmonary metastases were resected. The addition of L-MTP-PE resulted in progression-free survival, and that survival was better when L-MTP-PE was administered for a longer period. Copyright of the image is held by Paul Meyers. Used with permission from Paul Meyers

Progression-free survival was compared to a similar historical control group treated at MDACC with surgery and chemotherapy (Fig. 4). The median time to relapse for group 2 patients was 9 months compared to 4.5 months for the historical control group. Additionally, group 2 patients had a better outcome than group 1, supporting the concept that longer duration therapy with L-MTP-PE was superior. Since all patients who entered the trial had undergone resection of pulmonary metastases prior to study entry, it was possible to compare the histology of pulmonary metastases resected from study participants after treatment with L-MTP-PE to their own pulmonary metastases prior to the administration of L-MTP-PE [18]. Nodules resected following treatment showed peripheral fibrosis surrounding the tumor and inflammatory cell infiltration. This was evidence that L-MTP-PE had a biological effect on the tumor metastases.

Chemotherapy has been shown to be an essential component of the treatment of osteosarcoma [15]. If we wished to administer L-MTP-PE and chemotherapy concurrently to patients, we needed to show that chemotherapy did not interfere with the macrophage activation caused by L-MTP-PE and the L-MTP-PE did not interfere with chemotherapy. In *in vitro* studies adding monocytes activated by L-MTP-PE to cultures of tumor cells with serial concentrations of doxorubicin, there was no modification of the tumor response [19]. L-MTP-PE and chemotherapy were administered concurrently in three murine syngeneic models, and no additive toxicity was observed. Similar antitumor effects of chemotherapy were observed with and without L-MTP-PE [20].

Most importantly, Kleinerman and colleagues showed that doxorubicin did not interfere with cytokine release or activation of monocyte tumoricidal function by L-MTP-PE [19, 21]. They studied monocytes obtained from patients before, during, and after chemotherapy administration and showed no differences in the response to L-MTP-PE [22].

Investigators at MDACC and the Memorial Sloan-Kettering Cancer Center (MSKCC) performed a phase II study of concurrent administration of ifosfamide and L-MTP-PE in patients with metastatic pulmonary osteosarcoma that had recurred after initial therapy with surgery and multi-agent chemotherapy that did not include ifosfamide [23]. There was no increase in the anticipated toxicity of ifosfamide and no delays in administration of ifosfamide. Increases in cytokines following L-MTP-PE were similar to those seen when L-MTP-PE was administered as a single agent. Tumors removed from the lungs of patients following chemotherapy and L-MTP-PE showed both necrosis typically associated with chemotherapy and fibrosis and inflammatory changes previously reported following the administration of L-MTP-PE.

Prospective Randomized Phase III Trial

L-MTP-PE had demonstrated safety in a phase I trial. It had shown improved outcome compared to historical controls in a phase II trial. It was safe to administer concurrently with chemotherapy. It had shown significant improvement in survival in a prospective, randomized, double-blinded study in dogs with osteosarcoma. This evidence supported the development and design of a randomized phase III trial in osteosarcoma.

At the time that the phase III study was being designed there was another question of importance to the pediatric oncology community. Ifosfamide had been shown to be an active agent in patients with osteosarcoma which recurred following initial therapy, and objective responses were reported in 30–50 % of patients [24, 25]. Many investigators were using three chemotherapy agents to treat osteosarcoma: cisplatin, doxorubicin, and high-dose methotrexate. We designed a trial to answer two questions:

1. Would the addition of ifosfamide to cisplatin, doxorubicin, and high-dose methotrexate for the treatment of osteosarcoma improve the outcome?
2. Would the addition of L-MTP-PE to chemotherapy improve the outcome?

Osteosarcoma is a rare disease. In order to answer both questions in a reasonable period of time it was necessary to use a factorial design. In a factorial design, patients are randomly assigned for each intervention, but each intervention is analyzed for its effect on the entire population. Therefore, all patients who received ifosfamide (four-drug chemotherapy) would be compared to all patients who did not receive ifosfamide (three-drug chemotherapy), without considering whether or not they had been assigned to receive L-MTP-PE. All patients assigned to receive L-MTP-PE would be compared to all patients assigned not to receive L-MTP-PE, without considering whether they had been assigned to receive three- or four-drug chemotherapy. These marginal analyses rely on the assumption that no interaction exists between the two study interventions. No preclinical or clinical evidence suggested that there would be an interaction between the two study interventions and there was no plausible biological basis to suggest an interaction [22]. The final analysis at the completion of the randomized prospective phase III trial detected no interaction.

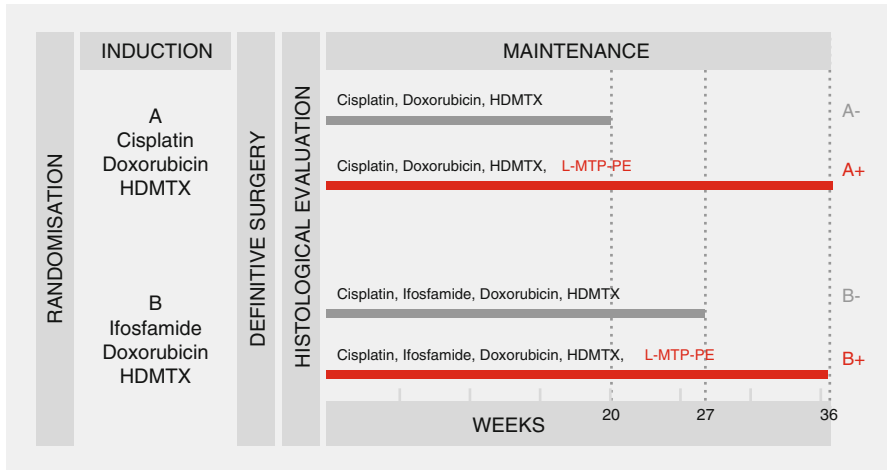


Fig. 5 The North American pediatric cooperative groups performed a prospective randomized trial in patients with osteosarcoma. Patients were assigned to receive chemotherapy with cisplatin, doxorubicin, and HD methotrexate (regimen A) or the same three agents with the addition of ifosfamide (regimen B). Total doses of cisplatin, doxorubicin, and HD methotrexate were identical in both regimens. Patients were randomly assigned at study entry to receive or not to receive L-MTP-PE, and L-MTP-PE was begun following surgical resection of the primary tumor and any sites of macroscopic metastatic disease. Copyright of the image is held by Paul Meyers. Used with permission from Paul Meyers

The study design for the chemotherapy question was an addition study (Fig. 5). Patients assigned to treatment arm A received cisplatin, doxorubicin, and high-dose methotrexate. Patients assigned to treatment arm B received the same agents with the addition of ifosfamide. Patients received an initial period of chemotherapy followed by definitive surgical resection of the primary tumor followed by additional adjuvant chemotherapy. Assessment of necrosis in the primary tumor after the initial period of systemic chemotherapy was performed as there is a strong correlation between the degree of necrosis in the primary tumor following initial therapy and outcome [26]. The duration of the chemotherapy prior to definitive surgery can influence the degree of necrosis observed at the time of definitive surgery [27]. Therefore the duration of the initial period of chemotherapy was the same in both regimen A and regimen B.

When to initiate L-MTP-PE therapy was a critical issue. All the preclinical and early clinical studies suggested that the efficacy of L-MTP-PE is linked to tumor burden and that maximum activity is seen in the setting of minimal residual disease [9, 23]. Roughly 80 % of patients with osteosarcoma present without clinically detectable metastatic disease as determined by conventional imaging. However, clinical studies clearly show that close to 90 % of these “non-metastatic patients” have microscopic metastases. This is the rationale for continuing chemotherapy following removal of the primary tumor. Unfortunately, despite the use of adjuvant chemotherapy following surgery 30–35 % of patients will relapse in the lung within 2 years.

Since L-MTP-PE has its maximum effect against minimal residual disease, L-MTP-PE therapy was initiated following surgical resection of the primary tumor. There were thus four treatment arms A, A+, B, and B+. Patients assigned to regimen A received chemotherapy with cisplatin, doxorubicin, and high-dose methotrexate. Patients assigned to regimen B received chemotherapy with the same three drugs with the addition of ifosfamide. Patients assigned to receive L-MTP-PE were designated with the addition of a plus sign to the chemotherapy regimen; 677 patients were randomly assigned to one of the four treatment regimens at the time of study enrollment. In retrospect, this was an error in study design, because it allowed for an imbalance in the assignment of poor-prognosis patients (as determined by % necrosis) to one arm, an error that ultimately masked the treatment success of L-MTP-PE in the three-drug plus L-MTP-PE group (A+) as discussed below.

There was no difference in the frequency of greater and lesser necrosis following initial chemotherapy between the patients assigned to chemotherapy regimens A and B. Toxicities were very similar among the arms of the study and were as anticipated from the chemotherapy regimen. We saw no increased toxicity from the addition of L-MTP-PE.

Analysis of the results of the study approximately 9 years after the last patient was enrolled (13 years after enrollment of the first patient) revealed the following:

1. Treatment with three chemotherapy drugs (regimen A) and four chemotherapy drugs (regimen B) achieved the same probability for both event-free and overall survival.
2. All patients assigned to receive L-MTP (with three- or four-drug chemotherapy) showed an improvement in event-free survival compared to those that received three- or four-drug chemotherapy alone. The probability for event-free survival 6 years from study entry was 67 % with L-MTP-PE and 61 % without. The *p*-value for this difference was 0.08.
3. The same comparison showed a statistically significant improvement in the overall survival. The probability for overall survival 6 years from study entry was 78 % with L-MTP-PE and 70 % without. The *p*-value for this difference was 0.03 (Fig. 6).
4. The hazard ratio for death from osteosarcoma comparing treatment with L-MTP-PE to treatment without was 0.7.

Necrosis following initial chemotherapy in the randomized prospective trial was analyzed according to the method described by Huvos [26]. Less necrosis (Huvos grade 1 and 2 necrosis) was associated with a higher probability for recurrence and death than more necrosis (Huvos grade 3 and 4). When we analyzed the frequency of greater and lesser necrosis among the patients assigned to receive each of the four possible randomized therapies, we observed an excess of patients with less necrosis assigned to receive three-drug chemotherapy in combination with L-MTP-PE (regimen A+) (Table 1). Since the observation of less necrosis strongly correlates with a higher probability for recurrence, this imbalance could explain the apparent failure to observe an improved outcome for event-free survival among the patients receiving three-drug chemotherapy who were assigned to receive L-MTP-PE.

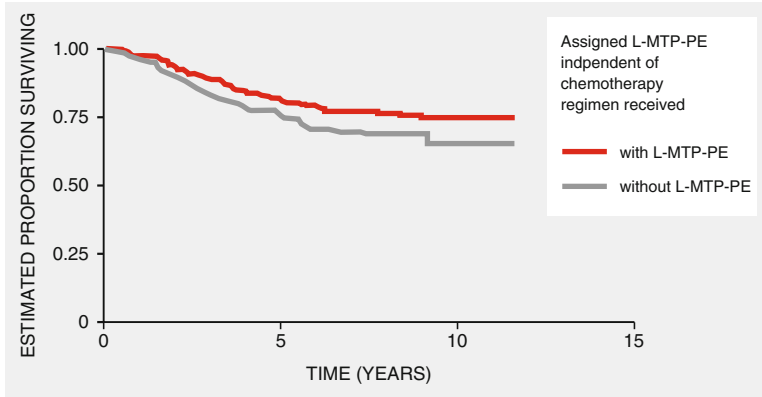


Fig. 6 Administration of L-MTP-PE was associated with improved overall survival. Patients assigned to receive L-MTP-PE following definitive surgery had a 78 % probability of survival of 6 years following study entry, compared with a 70 % probability for patients not assigned to receive L-MTP-PE ($p=0.03$). Copyright of the image is held by Paul Meyers. Used with permission from Paul Meyers

Table 1 Prospective randomized phase 3 trial: Imbalance in necrosis among patients assigned to treatment arms

Regimen	Huvos grade 1 and 2 necrosis		Huvos grade 3 and 4 necrosis	
	Unfavorable	Favorable	Not reported ^a	Total
A	78 (45 %)	71 (41 %)	25 (14 %)	174
A+L-MTP-PE	93 (56 %)	52 (31 %)	22 (13 %)	167
B	78 (47 %)	68 (41 %)	20 (12 %)	166
B+L-MTP-PE	73 (43 %)	72 (42 %)	26 (15 %)	171
Total	322	263	93	678

For the comparison between unfavorable and favorable necrosis among the treatment arms $p=0.08$

^aIncludes patients who progressed prior to definitive surgery or for whom data was not reported

Further analysis of the imbalance in necrosis revealed that by chance most of the imbalance took place in patients older than 16 at study entry. For patients aged less than 16 at study entry, there was better balance among the study arms in the frequency of patients with greater and lesser necrosis following initial chemotherapy (Table 2). This allowed us to examine the effect of the addition of L-MTP-PE to chemotherapy in 496 patients free from the confounding effect of an excess of patients with poor necrosis in one study arm. For this group of 496 children, the addition of L-MTP-PE to chemotherapy resulted in improved event-free survival (Fig. 7). The improvement was seen with both chemotherapy regimens to the same degree. There was no interaction between the two study questions. For this group, the addition of L-MTP-PE to chemotherapy resulted in improved overall survival (Fig. 8). The improvement was exactly the same for both chemotherapy regimens.

Table 2 Prospective randomized phase 3 trial: Balance in necrosis among patients less than 16 assigned to treatment arms

Regimen	Huvos grade 1 and 2 necrosis	Huvos grade 3 and 4 necrosis	Not reported ^a	Total
	Unfavorable	Favorable		
A	56 (43 %)	55 (42 %)	20 (15 %)	131
A+L-MTP-PE	63 (51 %)	43 (36 %)	16 (13 %)	121
B	60 (48 %)	52 (42 %)	12 (10 %)	124
B+L-MTP-PE	47 (39 %)	56 (48 %)	15 (13 %)	120
Total	225	208	96	495

^aIncludes patients who progressed prior to definitive surgery or for whom data was not reported

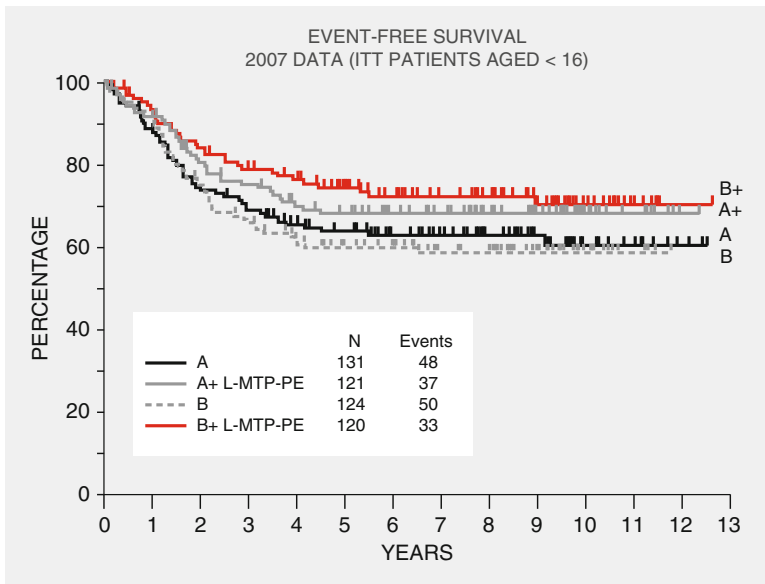


Fig. 7 Among 496 patients aged less than 16 years in whom there was no imbalance in necrosis following initial chemotherapy, administration of L-MTP-PE was associated with improved event-free survival with both chemotherapy regimens, and there was no interaction between the two study interventions. Copyright of the image is held by Paul Meyers. Used with permission from Paul Meyers

The hazard ration for death associated with the addition of L-MTP-PE was 0.5 ($p=0.001$). This analysis of 496 children in a prospective randomized trial represents one of the largest experiences ever reported for osteosarcoma and demonstrates a clinically and statistically significant improvement for both event-free and overall survival when L-MTP-PE is added to chemotherapy. The benefit was independent of the chemotherapy regimen to which the patients were assigned.

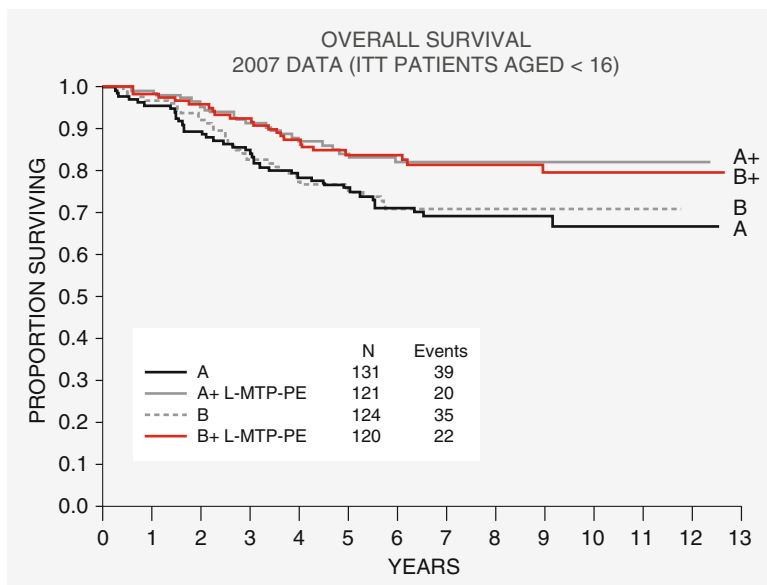


Fig. 8 Among 496 patients aged less than 16 years in whom there was no imbalance in necrosis following initial chemotherapy, administration of L-MTP-PE was associated with improved overall survival with both chemotherapy regimens, and there was no interaction between the two study interventions. The hazard ratio for death among this population in whom there was no confounding influence from an imbalance of patients with poor necrosis in one study arm was 0.5 ($p=0.001$). Copyright of the image is held by Paul Meyers. Used with permission from Paul Meyers

Phase III Randomized Trial for Patients with Metastatic Disease at Initial Presentation

For patients who do present with clinically detectable metastasis, the great majority have metastatic disease detected only in the lung. These patients can also be considered to have minimal residual disease burden after surgical removal of the primary tumor and all palpable pulmonary nodules. We elected to begin L-MTP-PE therapy for these patients at the time they were rendered free of clinically detectable metastatic disease, following surgical resection of the primary tumor, and pulmonary nodules for those patients. The results of the trial for this stratum were reported in 2009 [28]. The small number of patients enrolled in this stratum decreased the power of this stratum to detect statistically significant differences between treatments. We reported the following observations:

1. Similar to what we found in the study for “non-metastatic” patients, there was no interaction between the two study interventions seen in the patients in the metastatic stratum.
2. There was no difference in outcome between three-drug and four-drug regimens for either event-free or overall survival.

3. Both event-free and overall survival were superior for the patients who received L-MTP-PE than for the patients who did not, although neither analysis achieved a conventional level of statistical significance.
4. The hazard ratio for death from osteosarcoma comparing treatment with L-MTP-PE to treatment without was 0.7, exactly the same as the hazard ratio for patients with localized osteosarcoma.

Compassionate Access Trials

From 2008 to 2012 L-MTP-PE was administered to 205 patients with either osteosarcoma with metastases at initial presentation or patients with metastatic recurrent osteosarcoma after prior treatment with surgery and multi-agent chemotherapy. This was part of a compassionate access clinical protocol [29]. Patients received either L-MTP-PE as a single agent or L-MTP-PE concurrently with chemotherapy. Among 50 patients whose disease was completely resected, more than 50 % remained alive for more than 2 years from study entry. Many of these patients were treated following two or more recurrences after treatment with ≥ 2 prior lines of therapy.

Regulatory Status of L-MTP-PE

L-MTP-PE, marketed as MEPACT or mifamurtide, was approved by the European Medicines Agency in 2008 for newly diagnosed, non-metastatic osteosarcoma in conjunction with chemotherapy [30]. L-MTP-PE is currently included in the treatment of osteosarcoma in many countries in Europe, Central and South America, Israel, and Turkey. It remains an investigational agent in the United States.

L-MTP-PE is the only immune therapy to date to have received global approval for the treatment of a newly diagnosed sarcoma in conjunction with chemotherapy. The use of L-MTP-PE has had a clinically and statistically significant impact on the long-term survival of hundreds of children with osteosarcoma. Its toxicity profile is minimal when compared to chemotherapy. Its success warrants further investigation in other types of sarcomas and solid tumors that metastasize to the lung. The clinical success of L-MTP-PE also supports more focus on the macrophage as an immune cell target for therapy.

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