

# A Phase II Trial of Tetrathiomolybdate After Surgery for Malignant Mesothelioma: Final Results

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**Background.** Tetrathiomolybdate (TM) is an oral copper-depleting agent that has been shown to inhibit angiogenesis, and angiogenesis is a predictor of poor prognosis in malignant pleural mesothelioma. We hypothesized that cytoreduction of malignant pleural mesothelioma followed by TM will delay time to progression.

**Methods.** Between November 2000 and August 2003, 30 patients with malignant pleural mesothelioma received postoperative TM beginning 4 to 6 weeks after surgery at a dose adjusted to keep ceruloplasmin between 5 and 15 mg/dL. Time to progression was compared with the 55 stage I and II patients and 109 stage III patients previously treated with cytoreduction by one of us (H.P.).

**Results.** The 30 patients (25 men, 5 women; 13 stage I and II, 17 stage III), median age 67 years (range, 49–81 years), remained on TM a median of 14.9 months (range, 2 to 57 months). All patients reached target ceruloplasmin levels at a mean of  $34 \pm 2$  days (95% confidence interval, 30 to 39 days), and vascular endothelial growth

factor levels at baseline (ceruloplasmin =  $45.2 \pm 2$  mg/dL) decreased from  $2,086 \pm 390$  pg/mL to  $1,250 \pm 712$  pg/mL ( $p < 0.002$ ) at target ceruloplasmin ( $13 \pm 2$  mg/dL;  $p < 0.0001$  from baseline). The time to progression for all stage I or II TM patients was 20 months whereas that of 55 stage I or II non-TM-treated patients was 10 months ( $p = 0.046$  versus TM). No differences in time to progression for the stage III TM patients from surgery were seen (7 months).

**Conclusions.** Tetrathiomolybdate has antiangiogenic effects in malignant pleural mesothelioma patients after resection of gross disease, and exhibits minimal toxicity and comparable efficacy to previous multimodality trials. Tetrathiomolybdate should be evaluated for efficacy in combination with standard malignant pleural mesothelioma regimens, as well as for postsurgical maintenance therapy.

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Malignant pleural mesothelioma (MPM) remains an orphan disease in search of novel but hopefully efficacious therapies. It is generally concluded that cytoreductive surgery in selected patients can be performed safely in the hands of experienced surgeons [1], and the addition of systemic or other local therapies to the surgery has been shown to be safe and to improve survival at least for patients with less bulky, node-negative mesothelioma [2–9]. Nonetheless, mesothelioma invariably progresses in 90% to 95% of the patients and, for the most part, is uniformly fatal [1].

Targeted therapies for MPM are beginning to exploit novel molecular genetic findings that predict that molecules which interfere with receptors for tyrosine kinase pathways or bind proangiogenic molecules or their receptors could impact tumor growth [10]. The copper chelator tetrathiomolybdate (TM), which quickly and effectively depletes copper stores, is under investigation

as an antiangiogenic agent [11]. Previous work demonstrating that thiomolybdate promoted copper deficiency suggested that TM might be a useful agent in the treatment of Wilson's disease. Taken with meals, TM forms a tripartite complex of TM, copper, and food protein thereby preventing copper absorption. Given between meals, TM is absorbed into the blood, and forms a tripartite complex with TM, albumin, and the freely available serum copper, making the thus complexed copper unavailable for cellular uptake, and the amount of free copper is rapidly reduced [12]. The induction of copper deficiency by TM can be easily monitored by measurement of serum ceruloplasmin (Cp).

Tetrathiomolybdate has been evaluated in a phase I trial of TM in 18 patients with a variety of metastatic cancers including breast, colon, lung, and prostate [13]. Toxicity was minimal and included mild anemia and neutropenia, and a proportion of these advanced patients had stabilization of disease. Results of a phase II trial of TM in 15 advanced kidney cancer patients revealed that

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4 patients (31%) had stable disease for at least 6 months; none had a partial or complete response [14]. Serum levels of vascular endothelial growth factor (VEGF), basic fibroblast growth factor, interleukin 6, and interleukin 8 measured at the onset of copper deficiency were significantly reduced compared with pretreatment levels.

The most relevant cytokines and growth factors targeted by TM in angiogenic pathways are also active in mesothelioma and include the interleukin 6, interleukin 8, fibroblast growth factors, and VEGF [15-18]. Given the data that have emerged about the proangiogenic pathways in MPM as well as the ongoing investigations of TM as an antiangiogenic strategy, a phase II trial that investigated the impact of TM on time to recurrence after surgical cytoreduction was launched in November 2000. The specific aims of the study were to investigate whether TM could be given to MPM patients in an adjuvant setting safely on a long-term basis and maintain moderate copper deficiency as defined by serum Cp levels, and also to document time to progression and ultimate survival after surgery. In selected patients, serum VEGF levels were measured to document any effect of the drug on angiogenic cytokines.

## Patients and Methods

### Patient Populations

After approval by the Karmanos Cancer Institute and Wayne State University Human Investigation Committees, this study was launched in November 2000. Between November 2000 and August of 2003, 55 patients had exploration for mesothelioma at the Karmanos Cancer Institute. Seven of these patients had had preoperative chemotherapy, rendering them ineligible for the protocol. Of the other 48, 8 patients were found to have unresectable disease, 3 patients refused the protocol and were lost to subsequent follow-up, 1 patient sustained a postoperative nonfatal myocardial infarction, and 1 patient died in the postoperative period. One other patient was found to have an elevated calcium postoperatively as a result of a parathyroid cancer and was treated for this secondary malignancy. Four patients (3 biphasic, 1 epithelial) had histologic and radiographic progression postoperatively before study entry. None of these TM-ineligible patients were considered in the analysis of the historical group. This left 30 patients eligible and able to be evaluated (55%) for postoperative copper-reduction therapy during this period.

The cohort of 164 pathologic stage I through III patients having cytoreductive surgery for mesothelioma in the authors' previous experience from February 1990 to April 2005 was used to serve as an internal reference to compare to the TM cohort. Specifically, time to progression from surgery was used as a primary intermediate end point with survival as a secondary end point.

### Surgical Eligibility

Patients with histologically documented malignant mesothelioma who could tolerate pleurectomy or extrapleu-

ral pneumonectomy, both performed as a maximal cytoreduction along with a mediastinal lymph node dissection, were eligible for the trial if they had not had any previous therapy. All patients were surgically staged using the International Mesothelioma Interest Group staging system [19], incorporating the surgeon's personal observations (H.I.P.), operative, and postoperative pathology reports. After recovery from surgery, patients returned for induction of copper deficiency.

### Induction of Copper Deficiency

**TETRATHIOMOLYBDATE.** Tetrathiomolybdate was provided for this study by the University of Michigan in bulk lots suitable for human administration (Sigma-Aldrich Chemical Company, St. Louis, MO, and Milwaukee, WI). The TM was stored in 100-g lots under argon and was placed in 20-mg gelatin capsules for patient use. No other treatment including cytotoxic chemotherapy, molecularly targeted therapy, or radiation therapy was allowed while the patients were taking TM.

**MONITORING OF COPPER DEPLETION.** The serum Cp level was used as a surrogate measure of total-body copper status. As total-body copper was reduced, the serum Cp level proportionately decreased. The objective was to reduce Cp to 5 to 15 mg/dL of baseline, and to maintain this level for the course of the study. In previous trials, there appeared to be no untoward clinical effects from this degree of copper reduction that was termed "chemical copper deficiency."

**INDUCTION OF COPPER DEFICIENCY.** Four to six weeks after cytoreduction, patients returned for follow-up examination and baseline Cp measurement, complete blood count, and liver and renal function tests. Patients were then started on an induction dose of TM of 180 mg/day, given as a dose of 40 mg with meals three times a day, and then 60 mg away from food, generally at bedtime. Ceruloplasmin levels were monitored every week for the first 8 weeks of therapy (for out-of-state patients, the blood was drawn at home and sent in a overnight delivery postage-paid container), and then every 2 weeks thereafter. After achieving the target Cp, in most patients the first maintenance dose was 20 mg twice daily with meals and 40 mg at bedtime. Further modifications were performed aimed at maintaining Cp within a target window of 5 to 15 mg/dL and to prevent Cp values of less than 5 mg/dL. Ceruloplasmin levels were then performed every 2 weeks with monitoring for necessary dose adjustment. Patients were seen for history and physical examinations and toxicity evaluations every 2 months in follow-up.

### Toxicity

Toxicities were evaluated using the National Cancer Institute Common Toxicity Criteria 2.0. The first indication of true clinical copper deficiency is a reduction in blood cell counts, primarily anemia, as copper is required for heme synthesis as well as cellular proliferation. Thus, the copper deficiency objective of this trial was to reduce the Cp to 5 to 15 mg/dL, without decreasing the patient's hematocrit or white blood cell to below 80% of the

baseline value at entry. To maintain the Cp target and to prevent absolute Cp values less than 5 mg/dL, TM doses were adjusted as soon as possible once the Cp level was known. Tetrathiomolybdate was discontinued temporarily until hematocrit was restored to acceptable levels. If the hematocrit did not recover within 5 to 7 days of stopping the drug, the patient was transfused. Tetrathiomolybdate was discontinued and the dose adjusted if patients in the second stage of copper deficiency had acceptable hemopoietic indices (ie, >80% baseline) but had other grade 3 toxicities.

#### Vascular Endothelial Growth Factor Measurements

Blood was collected in a serum separator tube and was allowed to clot for 30 minutes before centrifugation at 1,000 g for 10 minutes. Serum was immediately frozen (-80°C) in aliquots of 1.2 mL in microcentrifuge tubes. Human VEGF enzyme-linked immunosorbent assay was performed as directed by the manufacturer (R&D Systems, Minneapolis, MN).

#### Disease Monitoring

All patients had pre-TM induction and follow-up computerized tomograms performed at the Karmanos Cancer Institute. Specifically, the computerized tomograms were performed within 1 week of starting TM (first postoperative computerized tomogram), when the target Cp level was reached, and then every 4 months as long as the patient was on the study. Any patient having physical examination or symptoms suggesting recurrent disease had radiographic or biopsy documentation at that clinic visit if it was between the 4-month follow-up period. Patients with documented recurrence had their TM discontinued and were counseled regarding other treatment options.

Table 1. Characteristics of the Tetrathiomolybdate and Historic Cohort

Patient Demographics	TM	Historic Cohort
Mean age (range)	66 ± 2 (49-84 y)	60 ± 1 (34-80 y)
Sex (male/female)	25/5	129/35
Histology		
Sarcomatoid	1	116
Biphasic	10	40
Epithelial	19	108
IMIG stage		
I	7	21
II	6	34
III	17	109
Lymph node status (involved/uninvolved)	10/20	66/98
Operation (pleurectomy/EPP)	11/19	72/92

EPP = extrapleural pneumonectomy; IMIG = International Mesothelioma Interest Group; TM = tetrathiomolybdate.

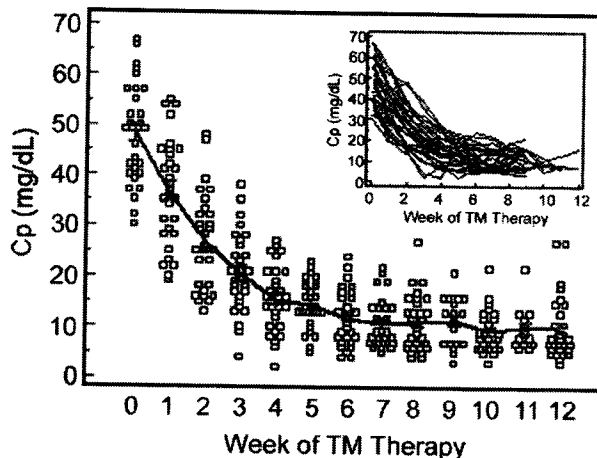


Fig 1. Mean ceruloplasmin (Cp) levels at inception of trial initiation and through induction. Inset, values for all patients during the induction period.

#### Statistical Analysis

The purpose of the trial was to determine whether the time to progression of patients after cytoreductive surgery could be significantly increased over the historic data for median time to progression for patients receiving surgery for mesothelioma determined by one of us (H.P.). If the median time to progression in the first 10 patients was not longer than this historic data, the study would have been closed. Survival time and time to progression was calculated from date of surgery until progression, death, or last follow-up as appropriate. All data are current to December 2007. The probability of survival or progression was calculated using the Kaplan-Meier method, and the significance of the difference between pairs of Kaplan-Meier curves was calculated using the Mantel-Haenszel procedure. Paired Student's *t* test evaluation of patients having both serum VEGF and Cp levels was performed using serum obtained before induction of TM and at the time of reaching the target Cp level.

#### Results

Characteristics of the patient populations are seen in Table 1. All patients in the trial recovered from surgery such that they were able to begin the induction dose of TM within 40 ± 2 days (range, 16 to 57 days) with no differences between patients having extrapleural pneumonectomy (40 ± 2 days) or pleurectomy (41 ± 2 days).

Once the induction dose of TM was started, all patients reached the level of copper deficiency as defined in this study at a median of 4.9 ± 0.3 weeks (range, 2 to 9 weeks; Fig 1). The Cp level at the start of the study was 48 ± 2 mg/dL (range, 30 to 67 mg/dL), and the mean Cp at 5 weeks was 14 ± 1 mg/dL (range, 2 to 23 mg/dL). Twenty-seven patients were maintained on the TM regimen until documented progression (range, 2 to 30 months), whereas 3 patients who did not have a

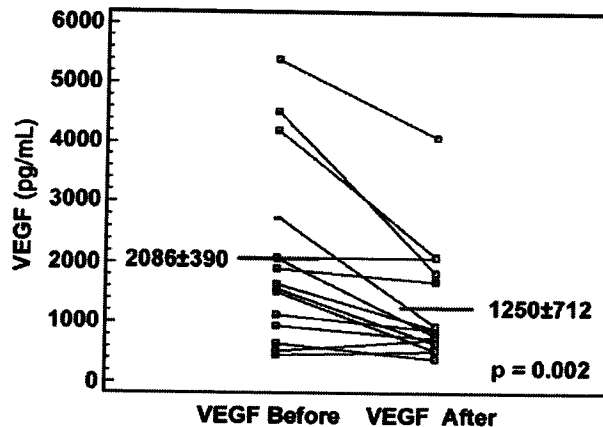


Fig 2. Influence of tetrathiomolybdate on serum vascular endothelial growth factor (VEGF) levels. Serum levels were analyzed before tetrathiomolybdate initiation and when target ceruloplasmin levels were reached.

recurrence had the TM discontinued when the protocol was closed to follow-up (61, 59, and 51 months from study entry).

#### Toxicity of Induced Copper Deficiency

All patients were able to be evaluated for toxicity, and for the most part, the TM was well tolerated. Dizziness unrelated to blood pressure or posture was a commonly seen adverse event (16 patients, 53%) during the induction phase to which the patients became acclimated. Grade 1 or 2 fatigue was reported by 90% of the patients. Sixteen (53%) of the patients had the TM held or reduced, most frequently because of grade 3 granulocytopenia (12 patients, 40%) with or without grade III anemia (4 patients, 13%) or thrombocytopenia (1 patient, 3%). The granulocytopenia reversed within 1 week of holding the TM in all cases, and the patients were then restarted on the drug at a reduced dose. There were no episodes of febrile neutropenia. Seven patients (4 extrapleural pneu-

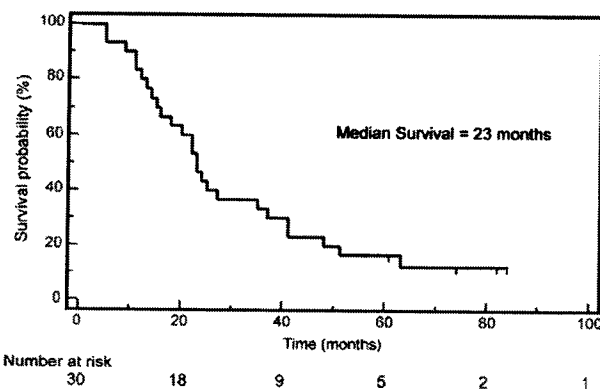


Fig 3. Survival from surgery for all tetrathiomolybdate patients. Survival of all 30 patients receiving tetrathiomolybdate and reaching ceruloplasmin levels of 5 to 15 mg/dL.

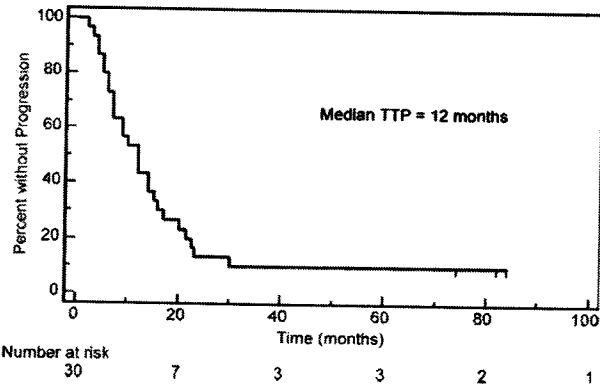


Fig 4. Progression from surgery for all tetrathiomolybdate patients. Time to progression (TTP) of all 30 patients receiving tetrathiomolybdate and reaching ceruloplasmin levels of 5 to 15 mg/dL.

monectomy, 3 pleurectomy) required red blood cell transfusion for the grade III anemia combined with grade II fatigue.

#### Vascular Endothelial Growth Factor Levels

Matching serum VEGF levels were measured after surgery, before institution of TM, and from the serum of 15 patients at the time of reaching their prescribed Cp level. A significant decrease in the serum VEGF levels was noted on reaching moderate copper deficiency (Fig 2).

#### Time to Progression and Survival

The median survival for all TM patients from surgery in the series regardless of stage was 23 months (1 year, 80%; 2 year, 43%; 3 year, 36%; Fig 3), and the median time to progression was 12 months (Fig 4). Four patients remain alive a median of  $64 \pm 2$  months from surgery. Three of these 4 patients are alive without disease. The time to

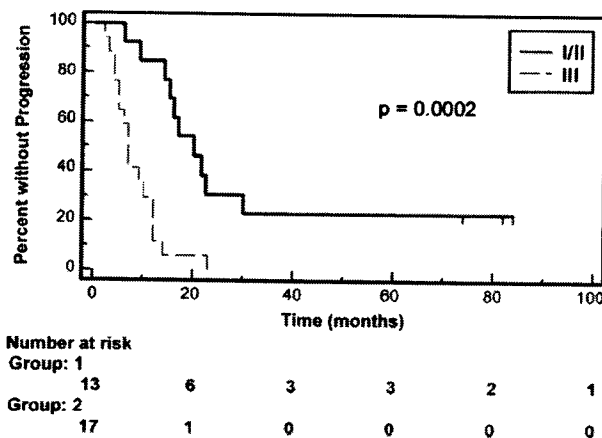


Fig 5. Progression from surgery for all tetrathiomolybdate patients, stage I or II (group 1; blue line) versus stage III (group 2; maroon line). Survival of all 30 patients receiving tetrathiomolybdate and reaching ceruloplasmin levels of 5 to 15 mg/dL by stage.

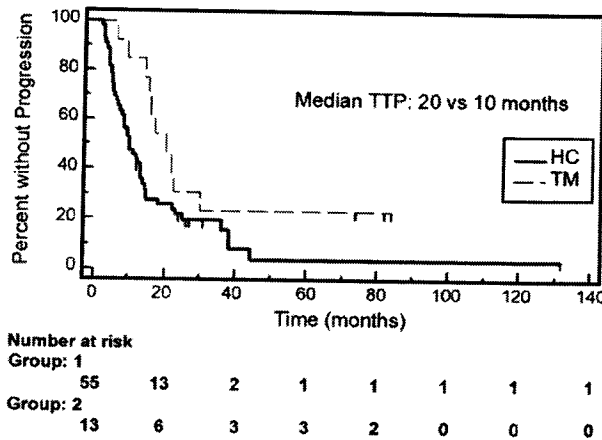


Fig 6. Progression from surgery for tetrathiomolybdate (TM; group 2; maroon line) versus historic cohort, stage I or II (HC; group 1; blue line). Time to progression (TTP) of stage I or II patients receiving tetrathiomolybdate and reaching ceruloplasmin levels of 5 to 15 mg/dL compared with historic controls.

progression for all stage I or II patients was 20 months, whereas the time to progression for the stage III patients from surgery was 7 months (Fig 5). In the historic cohort, the median time to progression for the 55 stage I or II non-TM-treated patients, whether they received adjuvant therapy at some point or not, was 10 months ( $p = 0.0046$  versus TM; Fig 6). In the evaluation of the data, 1 sarcomatoid patient occurred in the TM stage I or II group whereas there were 10 sarcomatoid patients in the stage I or II historic group. When the sarcomatoid patients were eliminated from evaluation of both groups, there was a significant increase in time to progression from 11 months to 17 months favoring the TM group. There was no significant difference in time to progression for the 17 stage III TM patients compared with the 109

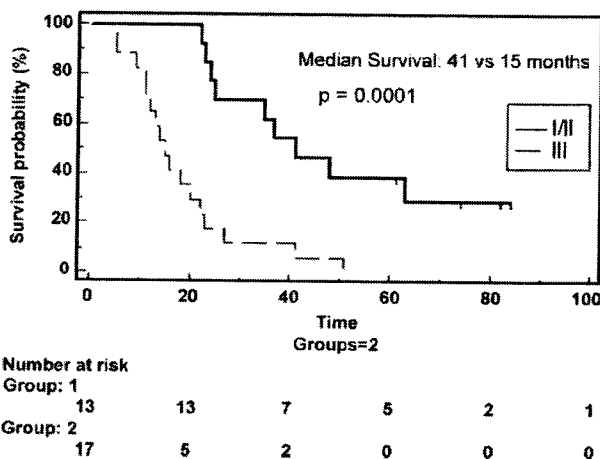


Fig 7. Survival from surgery for all tetrathiomolybdate patients, stage I or II (group 1; blue line) versus stage III (group 2; maroon line). Survival of stage I or II tetrathiomolybdate patients and stage III tetrathiomolybdate patients.

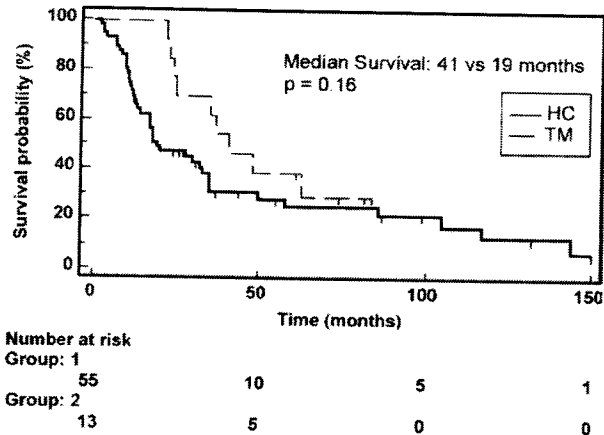


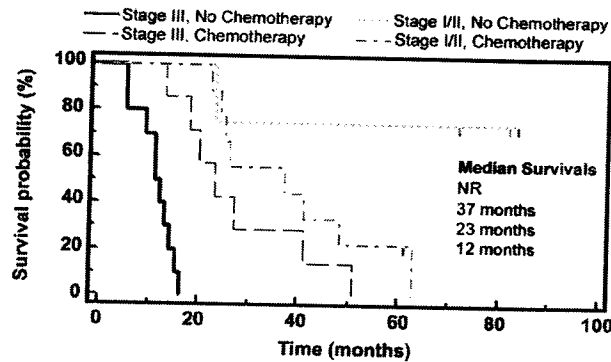
Fig 8. Survival from surgery for tetrathiomolybdate (TM; group 2; maroon line) versus historic cohort (HC; group 1; blue line), stage I or II. Survival of stage I or II patients receiving tetrathiomolybdate and reaching ceruloplasmin levels of 5 to 15 mg/dL compared with historic controls.

stage III historic cohort patients (both 7 months). The most common site of first recurrence was the ipsilateral chest ( $n = 14$ ), and other sites of progression included the abdomen with ascites ( $n = 7$ ), thoracoscopy or thoracotomy site ( $n = 3$ ), parenchyma of lung ( $n = 2$ ), and abdominal lymph nodes ( $n = 1$ ). All of the stage III patients experienced recurrence, whereas 3 of the stage I or II patients remain free of disease (1 biphasic, 74 months; 1 sarcomatoid, 84 months; 1 epithelial, 82 months).

For the patients treated with TM, the median survival for all stage I or II patients was 41 months (1 year, 100%; 2 years, 77%; 3 year, 57%) whereas that for stage III patients was 15 months (1 year, 65%; 2 year, 18%; 3 year, 12%; Fig 7). There were two non-mesothelioma-related deaths: 24 months after surgery in a 78-year-old stage I patient who died of a stroke 9 months after progressing and a 73-year-old stage III patient who died in an automobile accident 28 months after progression. There was a nonsignificant trend for decreased median survival (19 months;  $p = 0.16$  versus TM; Fig 8) for the 55 stage I or II non-TM-treated patients, whether they received adjuvant therapy at some point or not. No differences in survival were seen in stage III patients treated with or without TM.

#### Influence of Postprogression Adjuvant Therapy

All patients who progressed were given the option of receiving first-line mesothelioma chemotherapy, ie, Alimta and cisplatin or gemcitabine and cisplatin. Three patients remain alive without evidence of disease without receiving adjuvant chemotherapy or radiation in addition to their TM. Of the 27 patients who experienced recurrence, 16 received adjuvant therapy with Alimta and cisplatin ( $n = 16$ ; stage I or II, 9; stage III, 7), and



Number at risk					
Stage III, No Chemotherapy	10	0	0	0	0
Stage III, Chemotherapy	7	4	2	0	0
Stage I/II, No Chemotherapy	4	4	3	3	2
Stage I/II, Chemotherapy	9	9	4	2	0

Fig 9. Influence of salvage chemotherapy after progression for tetrathiomolybdate patients. Survival of tetrathiomolybdate patients by stage and adjuvant chemotherapy when tetrathiomolybdate was halted after progression. (NR = not reached; stage III, no chemotherapy = blue line; stage III, chemotherapy = maroon line; stage I/II, no chemotherapy = orange line; stage I/II, chemotherapy = green line.)

11 did not (10 stage III; 1 stage I or II). Figure 9 reveals that the best survival recorded has been for the patients with stage I or II mesothelioma who did not receive adjuvant therapy, and is heavily weighted to the 3 patients who, as of yet, have not experienced recurrence. The median survivals for the stage I or II and stage III patients receiving both TM and salvage chemotherapy were 37 and 23 months, respectively. These data compare favorably to the historic cohort of 21 stage I or II and 80 stage III patients who progressed after surgery and received adjuvant therapy as part of their multidisciplinary approach, who had a median survival of 18 and 12 months, respectively.

#### Comment

This study again demonstrates the feasibility of maintaining patients with cancer on an agent that induces a state of chemical copper deficiency. This study used such an agent after resection of a solid tumor (MPM) as the sole adjuvant treatment after surgery until evidence of progression occurred. Moreover, as with the earlier studies, the use of TM in the adjuvant setting was associated with minimal, reversible complications, which responded rapidly with the temporary suspension of the drug. Our data support the antiangiogenic mechanisms involved with TM as serum VEGF levels fell by 40% by the time the proposed serum Cp levels were met. We found no correlation between the VEGF level before initiation of TM and subsequent survival. This finding is

probably because of the small number of patients investigated with serum VEGF levels as well as the fact that these VEGF levels were obtained after surgical cytoreduction had been performed.

There are obvious methodological considerations that influence the interpretation of efficacy results for this trial. Because the majority of patients who experienced recurrence after receiving TM were treated with subsequent first-line chemotherapy in the adjuvant setting, survival end points must be reported by taking this additional therapy into account. Time to progression after complete cytoreduction, however, would only be influenced by initial stage of the tumor, completeness of cytoreduction, and a potential influence of TM. For patients with pathologic stage I or II, time to first progression from surgery was 20 months. In the literature, there are unfortunately few trials that discuss time to progression of mesothelioma after cytoreductive surgery based on pathologic stage at the time of resection. Therefore, although imperfect, we compared the mature data of the TM trial to the results of cytoreductive surgery from our personal experience. The 164 patients in this historic cohort group had complete demographic data including surgical staging, time to progression and time to death, and extensive details of their neoadjuvant therapy, adjuvant therapy, or radiation therapy. There was essentially a doubling of time to progression (10 months to 20 months) comparing the 55 historic stage I or II patients (of which 29 had received chemotherapy; time to progression, 13 months; 26 did not receive chemotherapy; median time to progression, 8 months). In the recent literature, the median time to progression in a large series of stage I or II extrapleural pneumonectomies [20] was 358 days, and this is similar to the 12.2 times median time to recurrence in the series from University of California San Francisco, which was predominantly stage I or II patients [21]. Hence, one can only state that the addition of this oral agent after surgery compares favorably (with respect to time to progression) to published series.

With regard to overall survival, one must not only compare our survival results with those for comparable MPM stages in the literature, but also take into account the influence of adjuvant Alimta and cisplatin. Surgery and hemithoracic radiation trials for MPM have reported median survivals of 33.8 months for stage I or II and 10 months for stage III [22]. From the series by Sugarbaker and colleagues [23] using surgery radiation therapy and chemotherapy, the median survival of 52 stage I patients was 25 months (which corresponded to stage I or II International Mesothelioma Interest Group staging) and 16 months for stage III patients. The data using TM with or without postoperative Alimta and cisplatin for stage I or II disease (median survival, 41 months) and stage III disease (14.5 months) compare favorably with these previously published reports, and in the design of comparative trials of TM to other therapies in the future, it is probably safe to conclude that the efficacy of postoperative TM with Alimta and cisplatin

is at least equivalent to data reported with other multimodality approaches.

Although the data for the use of this oral copper-reducing agent are encouraging, the reader must be cautioned that this was not a randomized trial, and the potential for unsuspected bias because of the inability to stratify comparison groups appropriately before the trial is administered is, by definition, compromised. Thus, it is important to validate this trial in a larger number of patients perhaps as a randomized phase II trial in comparison with the present standard of care in the future. Future trials with TM must validate whether the benefits seen in this study remain true in larger sample sizes, and must be able to seamlessly integrate TM into present trials that now routinely incorporate multimodality therapy for the disease. There is a trend toward a more aggressive approach with potentially resectable mesotheliomas that involves induction therapy with cytotoxic chemotherapy followed by surgery and radiation or more chemotherapy. The feasibility as well as efficacy of this approach in lengthening the time to progression and survival duration is being explored in phase II trials. Newer formulations of TM are being evaluated in phase I trials, and after the completion of these trials a larger validation trial in mesothelioma patients can be planned. Tetrathiomolybdate may be most beneficial for patients with minimal disease burden (such as after induction of a complete or partial remission), or concurrently with cytotoxic agents or modalities such as chemotherapy or radiation. Phase III trials that explore whether TM further lengthens the time to progression with presumed minimal residual disease could be possible in a multiinstitutional setting. Tetrathiomolybdate monotherapy would probably not be beneficial in patients with a large burden of MPM or rapidly progressive disease. In the metastatic setting, combination therapy has been well tolerated in animal models. Hence, phase II trials that investigate combination therapy of TM with chemotherapy or radiation therapy should be explored in patients with measurable disease to see whether response rates are influenced using TM in this setting. When at all possible, genomic data from tumors before and after therapy with TM should be generated to describe any predictive profile that defines a greater chance for remission using copper-lowering therapy.

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## DISCUSSION

**DR JOE B. PUTNAM** (Nashville, TN): Harvey, are there any other consequences of induced copper deficiency other than the dizziness and fatigue?

**DR PASS:** Those were the key ones. If you really want to delve into the data of how many patients had to have a blood transfusion because their hemoglobins actually go down because of suppression of the marrow, there were actually 7, I think, in the series who got blood transfusions, and they were having fatigue at the same time, and they were mainly the extrapleural pneumonectomy groups. So they got it, we then went back on the TM (tetrathiomolybdate), and then kept them on the TM until they progressed.

**DR MARK I. BLOCK** (Hollywood, FL): Harvey, that was beautifully presented and I think very exciting data. I'm anxious to see the phase III data. Hopefully it will come out at some time once you are able to get it done.

My question actually follows along the lines of what Dr Putnam just said, and that is, what about the other systems that depend on copper, and the enzyme that comes to mind is copper/zinc-SOD (superoxide dismutase), a constitutively expressed free-radical scavenger, which I would think would have some pretty important effects on a lot of things.

**DR PASS:** Well, we saw no liver toxicity. We saw no renal toxicity. I can't say that I have measured specifically Mn-SOD in my specimens that I've taken out of these patients. I think that's why this was done as a feasibility trial to begin with, because the only other trials that were done were phase I and phase II trials of renal cell cancer and then multiple histologies with a very similar profile of toxicity; fatigue, and a little bit of dizziness. This was the first trial that was done with this drug after surgery. So I've seen no other complications except what I have talked about. Maybe we'll see more when we have more patients.

**DR BLOCK:** I think it might be interesting. The copper/zinc-SOD is constitutively expressed, but the Mn-SOD is inducible,

so perhaps you may see a fall in copper/zinc but a rise in Mn-SOD to compensate.

**DR PASS:** I think that I need to add those correlates to future trials.

**DR DAVID C. RICE** (Houston, TX): Doctor Pass, that's a wonderful study and a great glimmer of hope to those of us who persist in treating this very, almost uniformly fatal disease.

My question relates to your historical control group. I certainly have been guilty in the past of perhaps not being as vigorous in my nodal dissection in my pleurectomy group. Certainly in your stage I or stage II patients who underwent pleurectomy, is it possible historically that some of those patients may have actually had stage III disease and that that may have influenced the survival curves?

**DR PASS:** That's a great point, David. Actually, since I started doing pleurectomy/decortications for mesothelioma back in 1990, I have done a complete mediastinal lymph node dissection on all those patients. Obviously I cannot comment on segmental lymph nodes and I cannot comment on N1 data unless they have had extrapleural pneumonectomies. So regarding the N1 data, there is probably going to be some missed, but I tried my best to at least look at the mediastinal situation.

**DR TODD L. DEMMY** (Buffalo, NY): Did you look for symptoms that might indicate the success of the therapy, for instance, like the rash of patients who receive tyrosine kinase inhibitors? Did any of these other symptoms of profound deficiency indicate that you're doing a good job suppressing VEGF (vascular endothelial growth factor)?

**DR PASS:** Well, Todd, as you well know, angiogenic inhibitors are mainly associated with hypertension, and in this situation, which works through a different pathway than the usual dual inhibitors, there was no hypertension that really happened with these patients, so it must be a different pathway.