Advances in Brief

Maintenance Biotherapy for Metastatic Melanoma with Interleukin-2 and Granulocyte Macrophage-Colony Stimulating Factor Improves Survival for Patients Responding to Induction Concurrent Biochemotherapy

Steven J. O’Day,1 Peter D. Boasberg, Lawrence Piro, Timothy S. Kristedja, He-Jing Wang, Maureen Martin, Regina Deck, Patricia Ames, Kelly Shinn, Hannah Kim, Patricia Fournier, and Guy Gammon


Abstract

Purpose: A prospective Phase II study of a novel maintenance biotherapy regimen after induction biochemotherapy was conducted in patients with metastatic melanoma in efforts to maintain responses and improve survival.

Experimental Design: Thirty-three patients with poor prognosis metastatic melanoma who achieved a partial response (PR) or stable disease (SD) to induction concurrent biochemotherapy were treated with chronic low-dose interleukin (IL)-2 and granulocyte macrophage-colony stimulating factor, and intermittent pulses of intermediate/high-dose decrescendo IL-2 over a 12-month period. The outcome of these patients was compared with a control group of patients at our institution who were treated recently with induction biochemotherapy and achieved a PR or SD.

Results: Five patients (15%) achieved a complete response, and 4 patients (12%) maintained SD for at least 6 months on maintenance biotherapy. The median progression-free survival (PFS) and overall survival (OS) were 8.1 months and 18.5 months, respectively, compared with historical controls, which were PFS 5.9 months (P = 0.0015) and OS 9.3 months (P = 0.0004). Administration of maintenance biotherapy was a significant predictor of PFS (P = 0.0008) and OS (P = 0.0001) in multivariate and matched-pair analyses (P = 0.002). The maintenance biotherapy regimen was well tolerated with no dose-limiting acute or cumulative toxicities.

Conclusion: In this single institution study, maintenance biotherapy with IL-2 and granulocyte macrophage colony-stimulating factor in patients achieving PR or SD to induction biochemotherapy improved PFS and OS compared with historical controls. A larger multicenter Phase II trial has been initiated in an effort to confirm these results.

Introduction

Over the past decade, multiple single-institution Phase II studies have demonstrated that the administration of multiagent chemotherapy with the biological response modifiers IL-23 and IFN-α, known as biochemotherapy, produces response rates of 40–60%. CR rates range from 10 to 20%, and median survival is 11–12 months (1–6). However, a significant limitation of biochemotherapy treatment is that the majority of patients who respond to treatment recur rapidly and succumb to their disease. Nearly 100% of patients who achieve a PR or SD to biochemotherapy progress within 12 months.

The median TTP for these patients (PR and SD) is <6 months, and median survival is 6–9 months (7–9). Therapy to prolong response duration is critical.

Clinical trials of IL-2 in melanoma suggest that chronic, low-dose s.c. administration results in the broad expansion of CTLs and natural killer cell populations (10–12). Clinically significant tumor responses require intermediate to high-dose IL-2 administration for sufficient immune effector cell activation (13–15). GM-CSF has been shown to stimulate peripheral blood monocytes/dendritic cells to become cytotoxic for melanoma cells in vitro (16). A recent melanoma Phase II clinical trial using adjuvant GM-CSF has been reported by Spitzer et al. (17) with encouraging preliminary results. When used in combination, IL-2 and GM-CSF have been shown to augment the proliferation of CTLs and increase the proportion of IL-2 receptor α chain-positive (CD25+) lymphocytes significantly more than either drug alone (18, 19). Studies in metastatic
melanoma have shown this combination to be well tolerated with preliminary evidence of antitumor activity (20, 21).

Based on this rationale, we developed a novel maintenance biotherapy regimen combining IL-2 and GM-CSF in patients who achieve a PR or SD to induction biochemotherapy. The regimen combines chronic low-dose stimulation of immune effector cells with IL-2 and GM-CSF, with intermittent pulses of intermediate/high-dose i.v. IL-2 for optimal effector cell activation.

**Patients and Methods**

**Patient Eligibility.** Patients with PR or SD to a cisplatin and IL-2-containing regimen of concurrent biochemotherapy for American Joint Committee on Cancer stage IV melanoma were eligible for study inclusion. Patients achieving CR to induction biochemotherapy were not eligible for study inclusion. The study required treatment to begin within 6 weeks of biochemotherapy completion. The study required treatment to begin within 6 weeks of biochemotherapy completion. CBC and differential, 12-channel biochemistry panel, and liver and thyroid function tests. CT of the chest, abdomen, and pelvis, and magnetic resonance imaging of the brain were performed within 4 weeks before treatment initiation. The study required treatment to begin within 6 weeks of biochemotherapy completion. CBC and differential, 12-channel biochemistry panel, and liver function tests were performed on days 1 and 15 during nonpulse IL-2 cycles, and on days 1, 3, and 17 during intermediate/high-dose IL-2 cycles. Thyroid function was monitored every 3 months.

Patients received a minimum of three cycles of study therapy unless there was evidence of clinically significant disease progression (as defined below) or irreversible grade III or IV toxicity. CT scans of the chest, abdomen, and pelvis were performed every three cycles, and magnetic resonance imaging of the brain every 6 cycles (3 cycles for prior CNS disease). At each evaluation, patients demonstrating SD, PR, or CR, and patients with nonclinically significant PD were eligible to receive an additional 3 cycles of therapy, up to a maximum of 12 cycles. All of the patients were followed for disease progression and survival at 3-month intervals for a period of 12 months. Subsequent follow-up was performed at 6-month intervals.

At any evaluation point, patients who met the criteria for systemic PD who did not suffer a decline in performance status were allowed to continue study treatment. However, for the purpose of study analyses, they were classified as PD. If subsequent restaging confirmed disease progression, patients were withdrawn from the study. If patients demonstrated CNS PD they were allowed to remain on study provided CNS lesions were treated with whole brain radiation, radiosurgery, or craniotomy, and patients restarted maintenance biotherapy.

**Table 1** Maintenance biotherapy regimen

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Agent</th>
<th>Dose</th>
<th>Frequency</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance Schedule&lt;sup&gt;a&lt;/sup&gt;</td>
<td>IL-2</td>
<td>1 MIU/m²</td>
<td>Daily: Monday–Friday</td>
<td>s.c.</td>
<td>1–28 (3–28 during pulse cycles)</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>125 mcg/m²</td>
<td>Daily</td>
<td>s.c.</td>
<td>1–14 (3–17 during pulse cycles)</td>
<td></td>
</tr>
<tr>
<td>IL-2 Pulse Schedule&lt;sup&gt;b&lt;/sup&gt;</td>
<td>IL-2</td>
<td>54 MIU/m² (Total)</td>
<td>Continuous Infusion</td>
<td>1–2 (Cycles 2, 3, 5, 6, 8, 10, and 12)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 18 MIU/m²</td>
<td>• Over 1st 6 hrs</td>
<td>i.v.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 18 MIU/m²</td>
<td>• Over 2nd 12 hrs</td>
<td>i.v.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 18 MIU/m²</td>
<td>• Over next 24 hrs</td>
<td>i.v.</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> 28-day outpatient regimen.

<sup>b</sup> 2-day inpatient infusion, followed by maintenance schedule for remainder of 28-day cycle.
within 6 weeks. Patients were required to discontinue all of the steroids 2 weeks before resuming maintenance therapy.

Response Assessment. CR was defined as the disappearance of all of the clinical evidence of tumor by radiographic studies and physical exam, followed by at minimum 4-week period without the appearance of new lesions. PR was defined as a >50% reduction in the sum of products of the perpendicular diameters of measurable lesions without the appearance of new lesions for a minimum of 4 weeks. SD was defined as a <25% increase in the sum of the products of the perpendicular diameters of all measurable lesions or a <50% decrease in the sum of the products of the perpendicular diameters of all measurable lesions without the appearance of new lesions for a minimum of 8 weeks. PD was defined as a >25% increase in the sum of the products of the perpendicular diameters of all measurable lesions, a 50% or greater increase in the size of any single lesion, or the appearance of any new lesion.

Historical Controls. The historical control group used in this study was selected from two published biochemotherapy trials conducted at the John Wayne Cancer Institute from July 1995 to August 1998 (22, 23). Seventy-six patients completed biochemotherapy before the initiation of the maintenance biotherapy study in May 1998. The control group comprised of all 34 of the patients who achieved either a PR or SD to biochemotherapy but did not receive maintenance biotherapy. All of the control patients and study patients were treated with identical inpatient concurrent biochemotherapy (DTIC, Cisplatin, Vinblastine, IL-2, and IFN). Control patients were treated with various doses of tamoxifen (20–340 mg) in the two published trials. The addition of tamoxifen to biochemotherapy did not improve response rate or median survival. Most study patients received tamoxifen in addition to biochemotherapy. A few of the more recent study patients did not receive tamoxifen when randomized trials failed to demonstrate improved efficacy with the addition of Tamoxifen to chemotherapy. Controls and study patients were followed identically for disease progression and survival.

Statistics. Overall survival and TTP were estimated according to the Kaplan-Meier method. Survival was measured from day one of biochemotherapy to date of death or last follow-up. TTP was measured from day 1 of biochemotherapy to the date of first evidence of PD by CT or physical exam criteria as outlined in “Response Assessment.” Comparison of survival was done using the log-rank test. Multivariate analyses of OS and TTP were performed using a Cox proportional hazards regression model of clinically important prognostic factors including sex, age, time from stage IV diagnosis to initiation of biochemotherapy, nonlung visceral sites of metastases, serum LDH, performance status, and prior therapies. All of the patients, study patients, and historical controls were included in the multivariate model. Matched pair analyses of OS and TTP were also performed. Historical controls and study subjects were matched according to baseline LDH (normal versus elevated), metastatic sites of disease (M1a/b versus M1c), and number of metastatic organ sites (≤2 versus >2). These criteria represent commonly cited predictors of overall and progression-free survival in metastatic melanoma (24, 25). The cutoff date for all of the study analysis was June 15, 2001.

Results

Patients. Thirty-three patients with stage IV melanoma were enrolled, beginning May 1998 and continuing through November 2000. All of the baseline characteristics (Table 2) were evaluated relative to the initiation of biochemotherapy to allow for better comparison with historical controls. Nineteen patients (58%) were enrolled after PR, whereas 14 patients (42%) achieved SD to biochemotherapy. The median age among study patients was 50 years (range, 17–70 years). The majority of patients (79%) demonstrated nonlung visceral sites of metastases, including 12 patients (36%) with liver involvement, 6 patients (18%) with bony metastases, and 6 patients (18%) with a history of CNS metastases. Thirty-two patients (97%) had two or more organ sites of metastases, including 18 patients (55%) with three or more metastatic sites. Among 32 patients with available data on baseline LDH, 16 (50%) exceeded the upper limit of normal (190 IU/liter) for our institution. Eight patients (24%) received adjuvant IFN for stage III melanoma before beginning biochemotherapy. Only 2 patients (6%) had received prior chemotherapy. Each of the baseline factors described previously is compared with historical controls (Table 2). Comparison of these factors reveals no statistically significant differences between study patients and historical controls, except for prior chemotherapy, as study patients were less likely to have had previous treatment with chemotherapy than controls (6% versus 24%; P = 0.05).

Treatment. A total of 186 cycles were administered to 33 patients, ranging from 1 to 12 cycles with a median of 4 cycles given/patient, and 109 of these cycles involved inpatient administration of high-dose i.v. IL-2. Two patients (6%) were unable to complete at least 1 cycle of maintenance biotherapy because of PD. Four patients (12%) failed to complete at least 3 cycles because of clinically evident disease progression. Nine patients (27%) completed at least 9 cycles of therapy, including 6 patients (18%) who completed the maximum 12 cycles. No patient was discontinued because of treatment toxicity.

On the basis of drug administration logs (available for 109 treatment cycles), there were 47 accounts in which study drug was not administered (43% of cycles). There were 21 cycles (19%) with 1 missed dose, and 10 cycles (9%) with 2 missed doses. Commonly cited reasons for missed doses included injection site reactions, patient error, and logistical or scheduling problems. Nine treatment cycles (5%) were delayed for 7 days or more. None were related to treatment toxicity.

Response. Five patients (15%) achieved complete resolution of all of the melanoma metastases while undergoing maintenance biotherapy (Table 3). All 5 of the CR patients were from the PR biochemotherapy response group. These patients had visceral sites of metastases with good performance status scores and normal LDH levels at the beginning of maintenance therapy (Table 4). At the time of analysis, June 15, 2001, 3 of the 5 patients who achieved CR to maintenance therapy were without metastatic disease (Table 4) at 17° and 35° months of follow-up. One of the CR patients had a local soft tissue recurrence at 10 months of maintenance therapy (14 months from day 1 biochemotherapy), which was surgically resected. This patient is currently without evidence of disease at 34+ months. Three of 5 CR patients developed CNS-only recurrences at 16, 13, and
The median time to disease progression among all of the study patients was 8.1 months, as measured from day 1 of biochemotherapy (Fig. 1). To date, 30 patients (91%) have experienced disease progression. Three patients (9%), 2 in CR and 1 with SD, completed study treatment and remain without evidence of PD at 35+, 17+, and 18+ months. Nine patients (27%) are alive with follow-up ranging from 12+ to 37+ months. The median follow-up among surviving patients is 30 months. The median overall survival among all of the study patients was 18.5 months (Fig. 1). Of 24 patient deaths, 9 (38%) were directly related to CNS metastases.

**Analysis TTP and Overall Survival.** Kaplan-Meier estimates of disease progression and survival revealed a significantly longer median TTP (8.1 months versus 5.9 months; \( P = 0.0015 \) by log-rank) and longer median OS (18.5 months versus 9.3 months; \( P = 0.0004 \) by log-rank) in study patients compared with historical controls. Multivariate analyses (Table 5) of disease progression demonstrated maintenance therapy \( (P = 0.0008) \) and elevated LDH \( (P = 0.02) \) to be independent predictors of overall TTP. TTP was also evaluated in multivariate analyses by systemic versus CNS-related disease progression. Maintenance therapy \( (P = 0.02) \) and metastatic involvement at more than two organ sites \( (P = 0.02) \) both predicted for systemic TTP. Elevated LDH was the only independent factor associated with CNS progression \( (P = 0.03) \). Maintenance biotherapy patients had a median time to CNS progression of 16 months compared with 11 months for controls, but this was not statistically significant \( (P = 0.19) \). Matched pair analysis showed favorable TTP for maintenance biotherapy patients in 23 pairs, compared with only 6 pairs for historical controls \( (P = 0.002) \).

Multivariate analyses of overall survival demonstrated maintenance therapy to be an independent predictor of prolonged survival \( (P = 0.0001; \text{Table 5}) \). Metastatic involvement at more than two organ sites \( (P = 0.001) \) and elevated LDH \( (P = 0.01) \) were predictors for poorer survival. On the basis of matched pair analysis, comparatively longer survival favored maintenance therapy in 21 pairs, and historical controls in 5 pairs \( (P = 0.002) \).

**Toxicity.** Common toxicities associated with intermediate/high-dose IL-2 administration included: constitutional symptoms, capillary leak syndrome, gastrointestinal toxicity,
Cumulative weight gain of 5–10 lbs was noted in 61 (56%) of 109 inpatient cycles. Weight gain of 10 lbs or more was seen in only 12 cycles (11%). Weight gain exceeding 20 lbs during any 1 cycle was not observed. No patient required i.v. IL-2 dose reduction or vasopressor support.

Outpatient toxicities were largely limited to grade 1 and 2 constitutional symptoms. Mild to moderate dermatologic toxicities were reported most frequently, as nearly all of the patients experienced IL-2/GM-CSF injection site nodules with associated erythema and pruritus. Mild to moderate urticarial reactions not requiring therapy were reported in 3 patients (9%). More severe urticaria was seen in 2 patients (6%) after intermediate/high-dose IL-2 and resumption of low-dose cytokine administration. These symptoms caused temporary discontinuation of study drug administration.

Hematologic toxicities were limited to intermittent thrombocytopenia, which most often coincided with the final day (day 3) of inpatient IL-2 administration. The median platelet count nadir for 109 cycles was 115,000/mm³. Grade 1 thrombocytopenia (>/=75,000–100,000/mm³) was observed in 18% of cycles, grade 2 thrombocytopenia (50,000–75,000/mm³) in 14% of cycles, and grade 3 thrombocytopenia (10,000–50,000/mm³) in 3% of cycles. Grade 4 thrombocytopenia (<10,000/mm³) was not observed. No platelet transfusions were required.

Thyroid function abnormalities were observed in 5 patients (15%). Three patients (9%) developed mild hyperthyroidism with suppressed thyroid-stimulating hormone levels. These patients were followed, and thyroid-stimulating hormone levels returned to normal without therapy. Two patients (6%) devel-

### Table 4  Characteristics of complete responders/stable disease

<table>
<thead>
<tr>
<th>Patient</th>
<th>MBT responsea</th>
<th>Southwest Oncology Group PSb</th>
<th>LDHb</th>
<th>Sites of metastasisb</th>
<th>No. sitesb</th>
<th>Current status</th>
<th>TTP (months)c</th>
<th>CNS/systemic PD</th>
<th>Survival (months)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CR</td>
<td>0</td>
<td>nl</td>
<td>Liver</td>
<td>1</td>
<td>EXP</td>
<td>16</td>
<td>CNS</td>
<td>28</td>
</tr>
<tr>
<td>4</td>
<td>CR</td>
<td>1</td>
<td>nl</td>
<td>Lung, liver, brain</td>
<td>3</td>
<td>NED</td>
<td>6</td>
<td>CNS</td>
<td>35</td>
</tr>
<tr>
<td>5</td>
<td>CR</td>
<td>1</td>
<td>nl</td>
<td>Lung</td>
<td>1</td>
<td>NED</td>
<td>14</td>
<td>Systemic</td>
<td>34</td>
</tr>
<tr>
<td>7</td>
<td>CR</td>
<td>1</td>
<td>nl</td>
<td>Intra-abdominal</td>
<td>1</td>
<td>AWD</td>
<td>13</td>
<td>CNS</td>
<td>28</td>
</tr>
<tr>
<td>9</td>
<td>CR</td>
<td>0</td>
<td>N/A</td>
<td>Lung</td>
<td>1</td>
<td>NED</td>
<td>N/A</td>
<td>17</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>SD</td>
<td>N/A</td>
<td>nl</td>
<td>Lung, bone, brain</td>
<td>3</td>
<td>EXP</td>
<td>21</td>
<td>CNS</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>SD</td>
<td>1</td>
<td>nl</td>
<td>Infracardiac, intra-abdominal</td>
<td>2</td>
<td>EXP</td>
<td>12</td>
<td>Systemic</td>
<td>18</td>
</tr>
<tr>
<td>8</td>
<td>SD</td>
<td>N/A</td>
<td>nl</td>
<td>Infracardiac, intra-abdominal</td>
<td>2</td>
<td>AWD</td>
<td>N/A</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>SD</td>
<td>N/A</td>
<td>nl</td>
<td>Intra-abdominal, brain</td>
<td>2</td>
<td>AWD</td>
<td>17</td>
<td>Systemic</td>
<td>37</td>
</tr>
</tbody>
</table>

a Abbreviations: MBT, maintenance biotherapy; nl, normal; NED, alive with no evidence of disease; AWD, alive with disease; EXP, expired; N/A, not applicable/available.

b At start of maintenance biotherapy.

c From day 1 of biochemotherapy.

### Table 5 Multivariate analysis of disease progression and survival

#### A. TTP

<table>
<thead>
<tr>
<th>Factors Associated with Time to Progression</th>
<th>P</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance Biotherapy</td>
<td>P = 0.0008</td>
<td>0.41 (0.24, 0.69)</td>
</tr>
<tr>
<td>Baseline LDH (Reference: LDH &gt; ULN)a</td>
<td>P = 0.019</td>
<td>1.86 (1.11, 3.11)</td>
</tr>
</tbody>
</table>

#### B. Overall survival

<table>
<thead>
<tr>
<th>Factors associated with overall survival</th>
<th>P</th>
<th>Risk ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance biotherapy</td>
<td>P = 0.0001</td>
<td>0.27 (0.15, 0.49)</td>
</tr>
<tr>
<td>No. of metastatic sites (Reference: &gt; 2 sites)</td>
<td>P = 0.001</td>
<td>1.64 (1.21, 2.21)</td>
</tr>
<tr>
<td>Baseline LDH (Reference: LDH &gt; ULN)a</td>
<td>P = 0.011</td>
<td>2.25 (1.21, 4.19)</td>
</tr>
</tbody>
</table>

a ULN, institutional upper limit of normal.

### Table 6 Summary of common inpatient toxicities (IL-2 pulse)

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Gradeb</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 1 2 3 4</td>
</tr>
<tr>
<td>Hypertension (89)b</td>
<td>12% 35% 42% 11%</td>
</tr>
<tr>
<td>Fever (96)</td>
<td>10% 83% 6%</td>
</tr>
<tr>
<td>Nausea (99)</td>
<td>1% 43% 55% 1%</td>
</tr>
<tr>
<td>Vomiting (85)</td>
<td>26% 65% 9%</td>
</tr>
<tr>
<td>Chills/rigors (82)</td>
<td>5% 83% 12%</td>
</tr>
<tr>
<td>Erythema (93)</td>
<td>15% 69% 16%</td>
</tr>
</tbody>
</table>

a According to Southwest Oncology Group common toxicity criteria.
b Number in ( ) represents data available out of 109 inpatient cycles.
c Percent of cycles.

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oped hypothyroidism requiring replacement therapy. Five patients (18%) developed new-onset vitiligo over the course of maintenance therapy. Survival for these patients ranged between 8 and 37+ months (8, 18+, 18, 30, and 37+ months). Four others (12%) demonstrated evidence of vitiligo at the completion of biochemotherapy, which persisted on maintenance therapy.

Discussion

The high response rate of biochemotherapy in patients with metastatic melanoma represents a promising advance compared with historical treatments with chemotherapy or biological agents alone. However, these biochemotherapy responses are short-lived with the majority of responding patients experiencing early progression and death after completion of treatment. This poor outcome, combined with the toxicity of treatment, has limited enthusiasm for biochemotherapy. To improve outcome, we tested a novel maintenance biotherapy regimen (IL-2 and GM-CSF) in an attempt to prolong survival in the poor prognosis subgroup of patients who achieve a PR or SD to induction biochemotherapy. Our results demonstrate a delay in TTP and an encouraging doubling of median survival in patients treated with maintenance biotherapy compared with recent historical controls.

These promising survival results must be viewed cautiously given the Phase II trial design and the nonrandom comparison with historical patients with potential unseen confounders. There was a trend for better ECOG performance status in comparison with historical patients with potential unseen confounders, Multivariate and matched pair analyses were performed. Both analyses revealed that the administration of maintenance biotherapy was a highly significant predictor of both progression-free and overall survival. We feel that this encouraging preliminary data are a strong rationale to proceed with a larger multicenter confirmatory trial.

As our ability to control systemic disease with induction biochemotherapy followed by maintenance biotherapy demonstrates, CNS PD remains a formidable challenge. More than 50% of study patients developed CNS progression within 18 months of initiating biochemotherapy treatment, and 38% of study deaths were directly related to CNS progression. Maintenance biotherapy appeared to have a more significant impact on time to systemic disease progression (P = 0.02) than CNS progression (P = 0.19). However, there was a trend for delay in CNS progression (16 versus 11 months) in maintenance patients. Because of the small size of the study, this important issue needs additional evaluation in a larger study.

We thank the Oncology Unit at Saint John’s Hospital for dedicated care of our patients. We also thank Ruth Weil and Jackie Kathe for their ongoing support of our research.

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