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A neoadjuvant biochemotherapy approach to stage III melanoma; analysis of surgical outcomes

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Abstract

Introduction—Completion lymph node dissection (cldn) and adjuvant therapy are recommended for node positive melanoma patients. The type and timing of systemic therapy remain unclear. We sought to analyze our institution's experience with neoadjuvant biochemotherapy in stage III melanoma patients.

Methods—Clinical information was extracted from a retrospective database on stage III melanoma patients. Eligible patients had tissue confirmation of stage III disease and administration of 2 cycles of biochemotherapy prior to their cldn. Overall survival was determined by social security death index.

Results—There were 153 patients available for analysis. Average depth of tumor was 2.5mm. Forty four percent of patients presented with clinical adenopathy whereas the rest had sentinel lymph node positive disease. Mean positive node count and total node count following cldn were 1.5 and 20. Surgical complications occurred in 23% of patients. Mean time between the initiation of neoadjuvant biochemotherapy to lymph node dissection was 48 days. Median follow up was 3.4 yrs. A significant toxicity or delay in treatment occurred in 79 patients (51%) during their neoadjuvant therapy. These patients had a worse overall survival but similar surgical outcomes when compared to those patients that tolerated the biochemotherapy without any adverse events.

Conclusions—Our data suggests that aggressive systemic treatment prior to lymph node dissection does not significantly impact surgical outcomes. The inability to tolerate this aggressive systemic treatment may predict a worse prognosis.

Keywords

Biochemotherapy; Neoadjuvant therapy; Lymph node dissection

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Introduction

The number of new melanoma cases worldwide is growing faster than any other malignancy. [1] For 2011 in the United States, there were 76,250 new cases, 9,180 melanoma related deaths and the estimated total direct cost associated with its treatment was \$291 million. [2]

Nodal status remains the most important predictor of long term survival. Patients with metastasis limited to their lymphatic basin have stage III disease. This represents an extremely heterogenous cohort of patients with a 5 year survival ranging from 23 to 87%. [3] Adjuvant systemic therapy is commonly recommended for stage III melanoma patients at high risk of developing metastatic disease. However the optimal type and timing of systemic therapy remain unclear. At our institution, in patients not otherwise eligible for a clinical trial, we have adopted a treatment strategy in which stage III patients receive systemic therapy, in the form of biochemotherapy, prior to and then following their completion lymph node dissection. We believe that our unique experience with this regimen may serve to establish a template for the future use of neoadjuvant therapy in stage III melanoma.

The effect of neoadjuvant systemic treatment on surgical outcomes in melanoma patients has not yet been studied. The aim of this study is to analyze the safety and efficacy of this treatment algorithm and to report its influence on surgical outcomes.

Materials and Methods

Patient selection

A retrospectively collected database was used to extract clinical and pathological information on stage III melanoma patients treated from 1998-present. This study was approved by our center's institutional review board. All patients underwent wide local excisions with appropriately negative margins and had tissue confirmation of nodal disease either through biopsy of an enlarged node or a sentinel lymph node. All stage III patients were imaged with a brain MRI and a PET scan, PET/CT scan or a CT chest, abdomen and pelvis to rule out distant disease. In order to receive biochemotherapy, patients required an ECOG performance status of ≤ 2 and adequate end organ function. Women of child bearing age consented to using birth control while undergoing treatment. Patients were excluded from biochemotherapy treatment if they were major organ allograft recipients, requiring steroids for a chronic illness, HIV+, pregnant or lactating or deemed medically unfit. Approximately one third of the patients included in this study were a part of a phase II multicenter trial of neoadjuvant biochemotherapy for stage III melanoma. [4] We queried the web based social security death index to obtain survival and date of death information on all the patients.

Treatment

Following confirmation of stage III disease, the patients proceeded with the administration of 2 cycles of biochemotherapy. This regimen consisted of cisplatin 20 mg/m² intravenously (IV) over 1 hour on days 1 to 4, DTIC 800 mg/m² IV over 1 hour on day 1 only, vinblastine 1.6 mg/m² IV push on days 1 to 4, IL-2 utilizing one of two schedules, most patients received 9MU/m²/day administered by continuous infusion a smaller number received 36 MU/m² via a decrescendo schedule over 4 days, IFN- 5 MU/m² subcutaneously days 1 to 5. Toxicities associated with the biochemotherapy were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0. Doses of medications were reduced or withheld for grade 3 or 4 toxicities usually hematologic, renal or hepatic.

After the administration of biochemotherapy, the patients were then restaged with imaging: a brain MRI and a PET scan, PET/CT scan, or a CT scan of the chest, abdomen, pelvis. If there was no distant progression of disease, patients were evaluated for completion lymph node dissection to be performed approximately 3–4 weeks following the last dose of biochemotherapy. Surgery was performed when constitutional toxicities had resolved and blood work was within normal limits. For patients presenting initially with adenopathy, tumor response to biochemotherapy was recorded after the first 2 cycles and described as complete clinical response, partial clinical response or stable disease according to standard oncologic criteria. Completion lymph node dissection was then performed. Days of drain use, surgical complications, number of positive nodes and total number of nodes were recorded.

Before initiating postoperative biochemotherapy, patients required evaluation and clearance from their surgical oncologist. Full recovery from their surgery was required: patients had to be receiving minimal pain medication, all drains had to be removed, and there could be no signs of infection. Two adjuvant cycles of biochemotherapy were then administered. After completion of treatment, patients were evaluated approximately every 3–4 months for 1 year and then every 4–6 months thereafter.

Patients were analyzed for toxicities, delays in treatment, surgical outcomes and event free and overall survival.

Results

Patients

One hundred fifty three patients were available for analysis from 1998 to 2009. Patient characteristics are shown in table 1. The mean age of the patients was 43 with a range from 17 to 76 years old and 57% of the patients were women. The mean depth of the primary was 2.3mm and 16 patients had ulcerated lesions. The majority of all primaries were located on either the trunk or extremity though 10% were in the head and neck region. More than half of all patients (86 patients) underwent a sentinel lymph node biopsy to diagnose their stage III disease whereas the rest, 44%, presented with adenopathy.

Of the 68 patients presenting with clinical adenopathy, 17 patients (11%) had an unknown primary, 42 (27%) patients presented with a locoregional nodal recurrence from a previously excised primary and nine of these patients presented concurrently with a melanoma primary and adenopathy.

The mean BMI was 27.3 and 26% of patients had a known significant comorbidity including hypertension, coronary artery disease, diabetes, or hyperlipidemia. The most common comorbidity was hypertension and 8% of all patients had multiple comorbidities.

Treatment

Approximately one third of all patients (n=45), either did not complete all four cycles or required a significant dose reduction of their biochemotherapy. All patients experienced flu like symptoms and required blood pressure support during treatment. Approximately 30% of patients had a significant toxicity from their biochemotherapy. A grade 3 or 4 hematologic toxicity was the most common (n=26) and the second most frequently occurring was a renal toxicity (n=20). Fifteen patients had a venous access related complication.

Surgical outcomes

Mean time from the start of biochemotherapy to the completion lymph node dissection was 48 days and from the surgery date to the start of adjuvant therapy was 31 days. For the entire cohort of patients, 23% had a postoperative complication with the most common being a wound infection. Mean drain time was 18 days.

Sentinel lymph node patients

Eighty six patients had a sentinel lymph node biopsy to diagnose their stage III disease. Pathology for the completion lymph node dissection was missing on 2 patients, leaving 84 patients available for analysis. Approximately 80% had no additional positive nodes at their completion lymph node dissection. The mean positive nodal count and total nodes harvested from the completion node dissection were 0.5 and 18.8. (table 2)

Clinical adenopathy

For patients who presented with adenopathy, their clinical response to biochemotherapy was documented after the completion of their neoadjuvant biochemotherapy and before their surgery (table 3). Fourteen patients had a palpable lymph node excised for diagnosis and this occurred prior to the initiation of their treatment. Three patients did not have a clinical response documented. Fifty one patients remained who had measurable disease which could be followed by clinical exam. Within this cohort, 45% (23 patients) remained with a stable exam while 27% (14 patients) had a complete clinical response i.e. no adenopathy was documented on physical exam at the end of their neoadjuvant biochemotherapy. No patient progressed either on imaging or on clinical exam while receiving neoadjuvant therapy. For those with a complete clinical response, the mean positive nodal count was <1 or 0.4. In the measurable disease cohort of 51 patients, 18 patients (36%) had no positive nodes in their completion lymph node dissection. For the entire group of patients with clinical adenopathy, including those patients without measurable disease, the average positive nodal count for the lymph node dissection was 2.7 and average total nodes harvested were 21. Forty percent of patients did not have any positive nodes in their completion lymph node dissection.

Adverse events secondary to neoadjuvant systemic therapy

Seventy one patients experienced at least one of the following: a significant toxicity during their biochemotherapy, a decrease in dosage or less than the 4 planned cycles, a significant delay between the start of preoperative biochemotherapy to the completion lymph node dissection. The delay in treatment was characterized as being greater than 1 standard deviation from the mean: > 61 days from the start of preoperative therapy to completion lymph node dissection. Please see table IV for summary of adverse events. The rest of the patients (n=82) completed all 4 cycles of biochemotherapy with the full doses recommended, did not suffer from any major toxicity and had no significant delay in their treatment. The median follow up for all patients was 3.4 years.

Subset Analysis

We compared the group of patients that experienced an adverse event during their chemotherapy to those that did not (the normal group). There was not a significant difference in age, comorbidities, BMI, tumor depth ulceration, or clinical adenopathy between groups. See table V.

We examined the surgical outcomes between groups. There was no difference in complication rate, drain time or positive nodal counts. The adverse event group did have a statistically significant greater number of total nodes harvested. See table VI.

For the entire group of 153 patients, 5 year event free survival was 61% and overall survival was 81%, with a median follow up of 3.4 years. When comparing the adverse group to the normal group, event free survival was 52% vs 68% ($p=0.09$) and the overall survival was 69 vs 91% ($p=0.005$). (figure 1)

Discussion

Our institution has established a practice in which neoadjuvant therapy is offered to stage III melanoma patients not otherwise eligible for a clinical trial. In the current literature, this is the first study reporting surgical outcomes in stage III melanoma patients receiving neoadjuvant treatment. By analyzing this experience we have come to several conclusions.

Expected surgical outcomes were not altered by the administration of neoadjuvant biochemotherapy. Our patient population was representative of those being treated at a tertiary cancer center: mean tumor depth was 2.3, greater than half (56%) received sentinel lymph node biopsies to diagnose their stage III disease while the rest presented with clinical adenopathy. Forty two patients (27%) had a history of melanoma and presented with a local regional lymph node recurrence. Average BMI and comorbidities of the patients studied were well documented and similar to national averages. Our analysis of the surgical outcomes in these patients were as follows: 26% of patients experienced a surgical complication, most commonly a wound infection, drain duration for an average of 17 days, and average positive nodes and total nodes removed at completion lymph node dissection were 1.6 and 20 respectively. These data are consistent with multicenter trials performed where neoadjuvant therapy was not used. [5–9]

In patients who presented with adenopathy, our data reinforces that biochemotherapy can result in an excellent tumor response. In the 51 patients that had measurable disease, 18 pts (36%) had a complete pathological response. In addition, we were able to show that a clinical response to the neoadjuvant therapy correlated well with a pathological response. The mean positive nodal count was <1 for the 14 patients that had a complete clinical response while it was 5.9 for the patients that had a stable or unchanged exam. If neoadjuvant therapy is used routinely in the future, the clinical response may provide a predictor of nodal involvement.

The benefit of neoadjuvant therapy has been demonstrated in the treatment of many operable cancers, including rectal, breast, ovarian and gastrointestinal stromal tumors. [10–13] This treatment strategy allows patients to potentially undergo a more conservative surgery, increases the probability of a negative margin resection, allows for the immediate treatment of subclinical metastatic disease, and provides both clinical and pathological evidence to the tumors in vivo response to systemic therapy. The benefits of neoadjuvant treatment must be weighed against significant risks: delays to definitive surgical resection, toxicities from the systemic treatment and potential increases in surgical morbidity.

The literature remains limited in the use of neoadjuvant therapy for stage III melanoma. Moschos et al studied the use of high dose intravenous IFN α -2b administered 1 month prior to lymphadenectomy in 20 patients with palpable disease. They found a 55% clinical response rate and a 15% complete pathological response rate. [14] A phase II multicenter study using neoadjuvant biochemotherapy with the same regimen as used in the current study showed that the 5 year relapse free survival and overall survival to be 64% and 78% respectively with a 26% complete pathological response in those with measurable disease. [4] A recent phase III trial comparing biochemotherapy to high dose interferon (IFN) was terminated early secondary to slow accrual, A futility analysis was performed and with a median follow-up of 49.3 months, neither the biochemotherapy nor IFN group had reached

median RFS or OS. There were no significant differences in estimated median RFS or OS between the two groups. [15] A larger intergroup study comparing biochemotherapy to IFN has been fully accrued and results are pending. Thus, biochemotherapy is not routinely used in the adjuvant setting and there is only limited data available on its neoadjuvant use for stage III patients.

Recent advances in the treatment of metastatic melanoma have established a role for CTLA-4 blockade. Presurgical antiCTLA-4 has been used for urothelial carcinoma of the bladder with a tolerable safety profile. In addition, biological data on the humane immune response was collected which guided the patients treatment. [16] Currently, antiCTLA-4 has only been tested in the adjuvant setting of stage III melanoma patients but this same neoadjuvant model has been proposed for study melanoma patients.

Biochemotherapy is an aggressive, cytotoxic systemic treatment. Our past experience with this regimen has reflected impressive response rates with a high but manageable toxicity profile. In our study, we separated the patients into 2 groups: those that had a major toxicity, change in dose/plan or a significant delay in their treatment (adverse event group) vs those that were able to tolerate this treatment regimen without any major problems (normal group). These groups were similar in their distribution: no significant difference in age, BMI, comorbidities, ulceration, tumor depth or number of patients presenting with clinical adenopathy. The surgical outcomes were not significantly different amongst groups: surgical complications, nodal counts and days of drain use were similar. We can conclude from these findings that the administration of an aggressive neoadjuvant therapy may lead to treatment delays and toxicities though should not significantly affect surgical outcomes.

Major toxicity during neoadjuvant biochemotherapy or a prolonged delay to surgical treatment was associated with a decreased overall survival. The event free survival was not statistically affected though. We were unable to determine here the reason(s) behind the worse prognosis in patients with adverse events. Various possibilities were considered. The simplest explanation is that the delay to surgery or the decrease in dose of the systemic agent due to the adverse event was the cause. We have also considered the possibility that those patients who had undetected metastatic occult disease were at higher risk for an adverse event. Alternately the adverse event itself may have predisposed patients to earlier and more frequent development of recurrent disease or death through immunosuppression or other mechanisms. Only further study can answer the question as to what mechanisms are involved. We can conclude however from these findings that the administration of neoadjuvant therapy may lead to treatment delays and toxicities, and if present, these may in turn result in a worse outcome. These delays in treatment and toxicities though do not appear to result from the surgical procedure or significantly affect surgical outcomes.

In the past several years, molecular discoveries have increased our understanding of melanoma tumor biology and have shown great potential for improved targeted therapies in melanoma patients. [18–20] Our research proposes a template to study these agents in both the neoadjuvant and adjuvant setting in patients with stage III disease.

Our data indicates that the administration of aggressive neoadjuvant therapy will not significantly impact surgical outcomes. In addition, given the impressive response rates, it may facilitate resection of bulky nodal disease. Despite potential toxicities and delays, neoadjuvant therapy can be delivered with acceptable surgical results. The inability to tolerate neoadjuvant therapy may predict a worse prognosis. With many promising medications currently under investigation, we offer our treatment experience as a model to test these new therapies in stage III melanoma patients.

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Fig 1.

Table I

Patient and Tumor Characteristics

Characteristic	No (%)
Total No. of patients	153 (100)
Sex	
Male	66 (43)
Female	87 (57)
Mean BMI	27.3
Significant comorbidity	40 (26)
Age, years	
Mean	43
Range	17–76
Location of primary tumor	
Head/neck	15 (10)
Trunk	39 (25)
Extremity	38 (25)
Genital	1 (<1)
Unknown	17 (11)
Tumor thickness, mm	
1.0	14 (9)
1.01–2.0	37 (24)
2.01–4.0	24 (15)
>4.0	18 (12)
Mean depth	2.5
Unknown primary	17 (11)
Clinical Adenopathy	68 (44)
Known primary	9 (6)
Unknown primary	17 (11)
Locoregional recurrence	42 (27)
Measureable disease	51 (33)

Table II

Extent of Lymph node disease at lymphadenectomy: sentinel lymph node positive vs patients with clinical adenopathy

No. of positive nodes	No. (std deviation)	Range	%
At lymphadenectomy for sentinel lymph node positive pts	84		55.6
0	67		79.8
1	17		20.2
Mean +nodes	0.5 (1.8)	0–12	
Median+	0	0–12	
Mean total nodes (std)	18.8 (11.4)	3–69	
Median total nodes	17	3–69	
At lymphadenectomy for pts with clinic adenopathy	67		44.4
0	27		40.3
>1	40		59.7
Mean + nodes (std)	2.7 (6.0)	0–37	
Median +	1	0–37	
Mean total nodes (std)	21.3 (14.5)	1–73	
Median	17	1–73	

Mean, median positive and total nodes at completion lymph node dissection after neoadjuvant biochemotherapy

Table III

Clinical and pathological response after 2 cycles of biochemotherapy in 51 patients with measureable disease

Clinical response	No. of patients	%	Mean No of Pathologically Positive nodes
Stable	23	45	5.9
Partial clinical response	14	27	1.4
Complete clinical response	14	27	0.4
Progression	0	0	

Table IV

Subset analysis: adverse event group versus normal group

Subset Analysis	
Groups	No.
Adverse event group	71
Delay	
Neoadjuvant therapy to clnd (>61 days)	19
Toxicity	59
Decrease in dose/ cycles	34
Normal group	82

Number of patients with delay in treatment, major toxicity, or decrease in dose/cycle while receiving biochemotherapy in the adverse event group

Table V

Comparison of patient and tumor characteristics in the adverse event group vs the normal group

Characteristic	Adverse event group (n=71)	Normal group (n=82)	P-value
Age (mean, std)	44 (13.6)	43 (11.5)	0.59
Comorbidities (n, %)	22 (31%)	18 (22%)	0.21
Mean BMI (std)	27.7 (5.4)	26.9 (5.6)	0.32
Mean Tumor depth (std), n	3.1 (2.7), n=49	2.3 (1.8), n=44	0.11
Ulceration (%)	10 (14.3%)	6 (7.5%)	0.25
Clinical Adenopathy (n, %)	27(38%)	41(50%)	0.14

Table VI

Surgical Outcomes in the Adverse group vs the normal group

Characteristic	Adverse event group (n=71)	Normal group (n=82)	P-value
Surgical complication (n, %)	19 (27.1)	16 (19.8)	0.28
Drain time (mean, std), n	18.5 (10.3), n=51	18 (10.8), n=64	0.83
+ nodes at clnd (mean, std)	2.2 (5.8)	0.9 (2.5)	0.08
Nodes	22.3 (15.0)	17.9 (10.5)	0.04