Adjuvant Therapy of Melanoma with Interferon-Alpha-2b Is Associated with Mania and Bipolar Syndromes

Gabapentin May Serve as a Mood Stabilizer

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BACKGROUND. The use of a high dose regimen of interferon-alpha-2b (IFN) has recently been demonstrated to benefit patients with resected high risk melanoma. The incidence of melanoma is rising rapidly, and the use of this regimen is becoming increasingly common. IFN has been associated with numerous psychiatric side effects.

METHODS. The authors describe four melanoma patients treated with adjuvant IFN who developed a manic-depressive syndrome or mood instability with therapy, and they review the literature on mania and the mixed affective syndromes associated with IFN.

RESULTS. The authors suggest that IFN may induce a mixed affective instability, and that patients risk developing hypomania or mania as IFN doses fluctuate or as IFN-induced depression is treated with antidepressants alone. Mania is particularly associated with dose reductions or pauses in IFN treatment. The risk of mood fluctuation continues after treatment with IFN stops, and patients should be monitored for 6 months following completion of therapy. Gabapentin appeared effective as monotherapy for acute mania, as an antianxiety agent, as a hypnotic, and as a mood stabilizer in these individual cases.

CONCLUSIONS. Mania and mood instability can occur in patients being treated with IFN therapy for melanoma. In this study, gabapentin was an effective mood-stabilizing agent for these patients. ***Cancer* 2000;89:356–62.**

KEYWORDS: medical oncology, melanoma, interferon, side effects, mania, mood instability, depression, gabapentin.

Interferon-alpha-2b (IFN) has been extensively tested as an immunomodulatory agent in patients with melanoma. IFN has been used in several clinical settings, including the treatment of patients with resected Stage II lesions (T3–4N0M0: melanoma depth between 1.5 and 3.99 mm [T3] and deeper than 4 mm [T4]), patients with Stage III disease (T1–4N1–2M0: melanoma of any depth with regional lymph node metastases), and patients with Stage IV melanoma (T1–4N0–2M1: melanoma with distant metastases). The staging reflects the 1992 American Joint Committee on Cancer guidelines, which are still generally used.

A variety of doses and schedules have been investigated. Adjuvant low dose IFN has been assessed in the treatment of Stage II[1,2] and III disease,[3] demonstrating prolongation of disease free survival (DFS) but not of overall survival (OS). The only randomized study that has demonstrated an OS benefit to IFN therapy in melanoma is the Eastern Cooperative Oncology Group (ECOG) 1684 study, in which

patients with Stage IIB and III melanoma were randomized to observation or to IFN-alpha-2b 20 mU/m^2 intravenously 5 days per week for 4 weeks, followed by 10 MU/m^2 subcutaneously 3 times per week for 11 months.[4] Median disease free survival and overall survival were both prolonged in the group of treated patients. In 1995, based on the results of ECOG 1684, the Food and Drug Administration approved the use of high dose IFN for Stage IIB and III melanoma.

In ECOG 1684, psychiatric perturbations were very common.[4] Of the 143 patients randomized to high dose IFN, 40% experienced depression, with 8% exhibiting Grade 3 depression (mood alteration interfering with activities of daily living) or Grade 4 (suicidal ideation). A better understanding of the mechanisms and types of depression experienced by these patients may lead to better treatment modalities for IFN-induced depression.

The existence of the neuropsychiatric effects of IFN has been recognized for over a decade.[5] Organic psychiatric syndromes were previously categorized in the treatment of viral hepatitis with IFN.[6] Electroencephalogram (EEG) changes, seizures, alteration of REM latency, and cholinergic dysregulation have also been documented in patients on IFN.[7] Valentine et al. reviewed the psychiatric syndromes associated with IFN administration to cancer patients.[8] Apathy, mental slowing, and fatigue were the most common manifestations of depression. With high intravenous doses, marked somnolence, lethargy, confusion, loss of taste and smell, and cognitive slowing occurred. Dysphoria, helplessness, and anhedonia (loss of interest in enjoyable activities) were seen later on during therapy. Suicidal ideation and severe dysphoria were noted at the beginning of treatment or at the time of dose escalation. Delirium, psychosis, and akathisia (pathologic restlessness) were reported, and, of particular relevance to this study, mania was also documented in patients receiving IFN.

Recently a prospective randomized study of the neuropsychiatric effects of IFN treatment in melanoma patients was reported by Caraceni et al.[9] In this study, 65 melanoma patients were assessed with a battery of neuropsychiatric measures at 1, 3, 6, and 12 months following diagnosis. Patients treated with IFN reported poorer concentration and more anxiety, fatigue, distractibility, depression, irritability, and nervousness. No differences emerged from evaluation of memory, concentration, thought processes, or cognitive performance. Hallucinations were reported in only two patients in the IFN group. This study provides prospective data to support the observation that the development of affective symptoms after the diagnosis of melanoma may be due to the institution of IFN therapy.

An underappreciated aspect of the profile of psychiatric complications from IFN therapy is the development of manic symptoms. Nine cases have been reported thus far in the literature and are reviewed in the "Discussion" section of this article. We review the courses of four patients with high risk melanoma referred for psychiatric treatment of mania while on adjuvant IFN. All patients gave their informed consent for the treatments received. A particular common feature of their course was the development of manic symptoms as the IFN dose was reduced or withheld. A regimen that could treat or prevent mania would improve quality of life during this treatment.[10] We found that gabapentin was useful as a mood stabilizer, as a treatment for insomnia and anxiety, as monotherapy for mania, and as preventative therapy against mania during treatment for depression.

Case 1

A woman was treated with adjuvant high dose IFN for an acral lentiginous melanoma. Depression occurred during IFN induction therapy. This was followed by hypomania in the maintenance phase, treated acutely with lithium. IFN treatment continued with gabapentin as a mood stabilizer for the remainder of the treatment course; brief euphoria, then depression, followed cessation of IFN and gabapentin.

At age 53 years, this woman presented with a melanoma of the thumb. Biopsy revealed an amelanotic melanoma at least 5.0 mm in thickness, with margins involved. She underwent a thumb amputation and an axillary lymph node dissection that revealed no metastases. Her past psychiatric history revealed no prior history of clinical depression treated with medications, although she had seen a psychiatrist at the time of a divorce.

She received standard adjuvant IFN therapy with an induction regimen of IFN 20 MU/m^2/day intravenously every day, Monday through Friday, for 4 weeks, and felt dysphoric. At the end of the month she experienced a brief episode of euphoria. During the second month of treatment, while on maintenance doses of IFN (10 MU/m^2 subcutaneously Monday, Wednesday, and Friday), she cried regularly, felt chronically anxious, and felt that she may as well be dead. She noted difficulty with concentration and reading. She was not suicidal.

IFN was withheld for 1 week and the patient was referred for psychiatric treatment. One dose of methylphenidate 5 mg led immediately to the onset of racing and desperate thoughts; in retrospect, we found that these had occurred intermittently for sev-

eral weeks prior to her initial evaluation. These symptoms resolved with 3 doses of perphenazine 4 mg. With the aid of lorazepam 1 mg orally 4 times a day, she began sleeping 6 hours per night. Lithium 300 mg twice a day was started, attaining a serum level of 0.8 mEq/L, and was discontinued after 1 week, when her mood stabilized. The narrow toxic-therapeutic ratio of lithium used in a patient with melanoma on IFN weighed against its further use. IFN was restarted, and morning anxiety returned with the second dose. Gabapentin was begun at 100 mg 3 times a day and titrated to 200 mg 3 times a day. At this dose, the morning anxiety disappeared despite continued IFN treatment. She was able to work for 7.5 hours per day. At the gabapentin dose of 300 mg in the morning, 200 mg midday, and 300 mg at bedtime, mild depression resolved. Her 8-hour serum gabapentin level at this dose was 3.1 μg/mL.

Over the remaining months of IFN therapy, the patient's mood remained stable. She developed worsening fatigue and anemia, requiring an IFN dose reduction in the seventh month of therapy. Upon completion of the IFN treatment, gabapentin and lorazepam were tapered off and discontinued over a 1-week period. The patient felt buoyant.

In the 3 months that followed, she was treated with 75 μg thyroxine for hypothyroidism that was detected by posttherapy blood work. Despite normalization of her thyroid indices, she developed hair trigger crying, dysphoria, anxiety, and loss of self-confidence. Sertraline 50 mg orally every day led to a complete and sustained remission of depression within 1 month of treatment initiation.

Case 2

A young woman underwent adjuvant high dose IFN therapy for Stage III melanoma. Five months into therapy she became manic when the dose of IFN was halved. Her mania responded to gabapentin monotherapy.

At age 25 years, this woman, who no previous psychiatric history, presented with a changing pigmented lesion on her back that on excision proved to be a Clark level IV melanoma. A sentinel lymph node biopsy was performed, which revealed a single involved lymph node, and after a negative axillary lymph node dissection adjuvant IFN was prescribed.

She underwent induction therapy, during which a single dose was held for leukopenia. She then began maintenance therapy with 10 MU/m^2 subcutaneously 3 times a week. In the fourth month of maintenance therapy, the IFN dose was reduced by 50% because the patient reported lethargy and weakness. Subsequent to this dose reduction, she developed marked insomnia. She became talkative, working on multiple crafts and writing a book, projects which she later characterized as "saving the world." She was referred for psychiatric evaluation for persistent insomnia and was diagnosed with hypomania. Gabapentin 900 mg 3 times a day was begun immediately and was subsequently tapered to 300 three times a day. Therapy led to an improvement in sleep and grandiosity. Her degree of mania decreased markedly. She developed insomnia when she ran out of medicine. The gabapentin dose was increased to and maintained at 600 mg 3 times a day, and the patient's mood remained stable during the following 8 months of IFN treatment.

Case 3

IFN therapy in a young man diagnosed with Stage III melanoma resulted in depression, but initiation of antidepressant treatment led to racing thoughts and increased anxiety. Gabapentin treated these symptoms and allowed successful antidepressant treatment with fluoxetine.

At age 20 years, this young man developed a 2.7 mm/Clark level IV melanoma on his lower back with concomitant left inguinal lymphadenopathy. Left inguinal lymphadenectomy revealed that 1 of 30 lymph nodes contained metastatic melanoma. A right inguinal lymph node dissection was negative. He did well without additional therapy for 12 years, at which time he developed abdominal discomfort and a palpable abdominal mass. A computed tomography (CT) scan revealed para-aortic lymphadenopathy. Head and chest CT were negative. It was not clear if the lymph nodes were contiguous with the lymph nodes resected 12 years before. Preoperative radiation therapy was employed, and at its completion the abdominal lymphadenopathy was fully resected.

After surgery he was treated with oxazepam 15 mg 3 times a day for anxiety. Adjuvant standard IFN was prescribed. He tolerated the induction therapy without dose reduction or delay and began maintenance therapy of 10 MU/m^2 3 times a week by subcutaneous injection. During the fifth month of therapy he became depressed, lost his motivation, and became very anxious. His IFN dose was halved to 5 mU/m^2 3 times a week, and he was referred for psychiatric evaluation for depression.

Fluoxetine 20 mg was started. After 3 days of therapy, he developed racing thoughts, anxiety, and a feeling of being energized. Fluoxetine was withheld and gabapentin 300 mg 3 times a day was started. Fluoxetine 10 mg was reinstituted without a return of racing thoughts. Depression resolved briefly and then recurred. An increase in fluoxetine to 20 mg every day was again associated with symptoms of anxiety. After

gabapentin was increased to 600 mg 3 times a day, the dose of fluoxetine was increased to 20 mg every day without further difficulty, and the symptoms of depression resolved.

After a month of reduced IFN dosing, and with the improvement and stabilization in his mood on 600 mg gabapentin 3 times a day, the IFN was gradually increased to full dose. For the remaining months of treatment, mood was stable on fluoxetine 20 mg every day and gabapentin 600 mg 3 times a day.

Upon completion of IFN therapy, he became talkative and began "compulsively doing one project after another." Fluoxetine dose was reduced to 10 mg every day and gabapentin was maintained at 600 mg 3 times a day.

Case 4

A young man was treated with adjuvant IFN for a deep primary melanoma and developed insomnia and depression. Gabapentin helped with his insomnia and led to moderate improvement in the depression, but depressive symptoms worsened after completion of IFN therapy. Fluoxetine successfully treated his depression.

At age 24 years, this man presented with a 6.0 mm/Clark level IV melanoma of the back. Lymphoscintigraphy revealed drainage to both axillae and both inguinal regions, so a sentinel lymph node biopsy was not performed. Six months later he developed right axillary lymphadenopathy, and at the time of operation 2 of 27 lymph nodes were found to contain metastatic disease.

High dose adjuvant IFN was prescribed. During induction therapy, IFN was held several times for hepatotoxicity. Five months into therapy he reported fatigue and insomnia. He was started on gabapentin 200 mg 3 times a day and lorazepam 1 mg at bedtime as treatment for his insomnia. After 8 months he began to have difficulty making decisions, a lack of motivation, depression, and poor concentration. His appetite was stable, and he was not anxious. His mood improved with an increase in gabapentin dosing to 600 mg 3 times a day; the agent attained a serum level of 2.3 μg/mL. At 1 year, IFN therapy was stopped and gabapentin was tapered. Insomnia, irritability, a sense of worthlessness, and a loss of libido developed during the following 6 weeks. Fluoxetine 20 mg led to a response with a marked improvement in his mood for several months before his death from recurrent disease.

DISCUSSION

The IFN-induced manic depressive syndrome is likely underdiagnosed. Depressive and anxious symptoms are often attributed to the trauma of the cancer diagnosis or the flulike syndrome of IFN treatment. Euphoria and unexpected energy are associated with the relief of stopping IFN treatment, and these symptoms may be viewed by the oncologist as normal. In fact, they can cause a substantial detriment to the patient's quality of life. Depression, irritability, and anxiety are often coincident with mania, and mixed presentations are common. Only when the suffering or change of behavior is extreme is it fully recognized and is referral to a psychiatrist made. We note that many of the discrete symptoms listed by Valentine et al.[11] to describe IFN-induced neurotoxicity are characteristics of bipolar disorder. Distractibility, irritability, hallucinations, strange thoughts, and mood swings can be grouped with mania. Loss of interest in people, activities, food, or sex; loss of motivation or emotion; decision-making difficulty; and slowed movements are associated with depression. Anxiety, restlessness, insomnia, and tension could be present in both.

Based on these observations, we conclude that IFN therapy induces mood instability, which encompasses the symptoms of anxiety, depression, and hypomania. We propose that these variable manifestations during IFN treatment may be interpreted as a mixed manic or dysphoric manic and depressive syndrome and be treated as such by a psychiatrist. In our experience, the onset of this mood instability varied from patient to patient. In the above-documented patients with high risk melanoma, depression occurred during treatment with IFN or with initiation of treatment; and mania occurred upon cessation of IFN, upon lowering the IFN dose, or after initiation of antidepressant treatment for IFN-associated depression (Table 1). Mixed presentations occurred along the way. In several cases mood continued to fluctuate after treatment with IFN had stopped.

Nine other case histories of patients who developed mania while on IFN have been recorded,[5,12–16] and these provide additional examples of the manner in which mania can present in patients receiving this agent. In several of these cases, the onset of mania occurred after changes in IFN dosage or after pharmacologic treatment of depression. These cases are summarized in Table 2.

Because of the association between IFN therapy and mood disorders, many physicians are reluctant to prescribe IFN to patients with an antecedent psychiatric history or a strong family history of mood disorders. We feel that a pretherapy history of psychiatric disorders is not a contraindication to treatment with IFN-α. Rather, patients with a past history of psychiatric disorders of any sort, patients having a first-degree relative with a history of manic depression, and

TABLE 1
Major Features of Affective Instability during Interferon Treatment for High Risk Melanoma

			Mania, hypomania			Depression		
Case	Months on IFN	Month referred	Coincident with dose reduction	Coincident with antidepressant (type)	Anxiety	With IFN	Post-IFN	Response to gabapentin
1	12	2nd	Yes	Yes (methylphenodate)	Yes	Yes	Yes	Stable mood
2	12	4th	Yes	No	No	Yes	No	Resolution of acute mania
3	12	5th	Yes	Yes (fluoxetine)	Yes	Yes	No	Resolution of acute mania
4	12	5th	No	No	Yes	Yes	Yes	Resolution of anxiety/dysphoria

IFN: interferon-alpha-2b.

TABLE 2
Case Reports of Interferon-Induced Mania

				Mania, hypomania			Depression	
Case (reference no.)	Disease type	IFN dose	Mos on IFN (at onset of mania)	Coincident with dose reduction	Coincident with antidepressant (type)	Anxiety	With IFN	Post-IFN
1[12]	Hepatitis B	10 MU SC TIW	1	Yes	No	Yes	Yes	Yes
2[12]	Hepatitis B	10 MU SC TIW	1	Yes	No	No	Yes	No
3[13]	Chronic myelogenous leukemia	8 MU SC QD	31	Yes	No	No	Yes	Not known
4[13]	Chronic myelogenous leukemia	Not known	24	Yes	No	No	No	No
5[14]	Chronic myelogenous leukemia	6 MU SC QD	5	No	Yes (amitriptyline for insomnia)	No	No	No
6[15]	Chronic myelogenous leukemia	9 MU SC QD	4	No	No	No	No	Yes
7[16]	Hepatitis C	9 MU SC TIW	1	No	No	No	No	Yes
8[24]	Essential thrombocythemia	3 MU SC BIW	48	Not known	No	No	No	No
9[5]	Chronic myelogenous leukemia	3 MU IM QD	1	No	Not known	Not known	Not known	Not known

IFN: interferon-alpha-2b; MU: million units; SC: subcutaneously; IM: intramuscularly; TIW: 3 times a week; QD: every day; BIW: twice a week.

patients with an overall strong family history of psychiatric disorders should undergo a pretreatment psychiatric evaluation and have close psychiatric follow-up during therapy to detect and manage IFN-related mood disorders.

Treatment with IFN will almost always have some effect on a patient's functional capacity and a patient's mood. Referral to a psychiatrist should be made when mood changes interfere with the patient's ability to function at work or at home and if other cardinal signs of depression or mania manifest themselves. For depression, these include tearfulness, anxiety, hypo- or hypersomia, anhedonia, feelings of hopelessness, and suicidal ideation; for mania, they include hyperactivity, racing thoughts, and grandiosity. The role of brain imaging in the context of these behavioral changes is controversial. Although metastatic brain lesions rarely present with the classic findings of depression or mania, case reports do exist.[17] Because melanoma metastases first present as central nervous system lesions in approximately 10% of cases, one could consider imaging the patient for mood changes, especially if these occur in the context of headaches or other neurologic symptoms.

Gabapentin has been effective therapy in the treatment of anxiety disorder[18] and has been used as a mood stabilizer in cases of resistant manic depressive disease.[19,20] However, its effectiveness as an antimanic agent or a mood stabilizer has not been established systematically over time. In this study, we show that gabapentin may be helpful in treating mania associated with IFN therapy. In our 4 cases, gabapentin was effective as monotherapy for mania, as an antianxiety agent, and as a mood stabilizer (Table 1). Doses used here tended to be low, in the 900–1800 mg/day range, compared with doses up to and exceeding 2700 mg/day when used as an antiseizure medication or as therapy for diabetic neuropathy.[21] In our patient group, gabapentin did not fully treat depression, with one patient subsequently demonstrating a better antidepressant response while on fluoxetine. Increasing gabapentin dosage at the time of IFN dose reduction may be an effective strategy to prevent hypomania. Ideally, a psychiatrist should prescribe gabapentin. This will allow for optimal management of the patient's psychiatric symptoms, with the addition of other pharmacologic agents as needed.

Gabapentin has a favorable side-effect profile. For gabapentin doses titrated 900–3600 mg, common adverse events are dizziness, somnolence, and nausea, but the agent is generally well tolerated. Doses are adjusted for renal impairment, and it is safe in overdose. It has less liver toxicity than valproate, less hematologic toxicity than carbamazepine, and less neurotoxicity than lithium; this is important because IFN itself causes hepatic, neurotoxic, and hematologic toxicity.

The etiology of IFN-induced mood disorders is not well understood. A recent report by Rapaport et al. suggests that a correlation exists between immune stimulation and the occurrence of mania.[22] Manic bipolar patients may have increased levels of autoantibodies, changes in phenotypic lymphocyte profiles, and leukocytosis relative to normal controls. There is also a trend toward increased levels of soluble interleukin-2 and soluble interleukin-6 receptor levels in patients with mania.[22] These data suggest a possible role for the immune system in modulating mood, and IFN may act as an effector molecule. On the other hand, Abe et al. recently demonstrated that chronic administration of IFN-α to Wistar rats increased the avidity of low-affinity serotonergic receptors in rat brain.[23] Abnormalities in serotonergic receptor function have been implicated in the pathogenesis of mood disorders in humans and suggest another etiologic mechanism for IFN-mediated neurotoxicity. The manner by which gabapentin modifies the neuropsychiatric side effects of IFN is not known.

In summary, we suggest that the affective toxicity of IFN be viewed as mixed affective instability with a risk of hypomania or mania as doses fluctuate or as depression is treated with antidepressants alone. Mania is particularly associated with dose reductions or breaks in IFN treatment. Gabapentin may be useful as a mood stabilizer. The risk of mood fluctuation continues in the months after treatment with IFN stops, so patients should be monitored for several months following treatment cessation.

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