Cytokine-Based Therapy and Biochemotherapy for Advanced Melanoma

Michael B. Atkins

Abstract
A variety of immunotherapeutic approaches have shown activity in patients with metastatic melanoma with the best results being observed with interleukin 2 (IL-2). Follow-up data through 2004 confirm the durability of responses produced by the Food and Drug Administration – approved high-dose IL-2 regimen in this patient population. Efforts to develop more tolerable and/ or effective IL-2 – based treatment regimens by either prolonged administration of lower doses or the combination of IL-2 with other cytokines, monoclonal antibodies, or vaccines have yet to produce results superior to those seen with high-dose IL-2 alone. Recent investigations have suggested that, in some patients, IL-2 may expand regulatory T-cell populations leading to immune tolerance rather than antitumor immunity. Efforts to shift this balance in favor of immune rejection by reducing the confounding effects of regulatory T cells on IL-2 therapy or the use of novel and potentially more purely immunostimulatory cytokines are ongoing. Despite promising phase 2 data, phase 3 studies have failed to show meaningful clinical benefit for the combination of cytokines with cytotoxic chemotherapy, so-called “biochemotherapy.” Nonetheless, recent investigations with biochemotherapy followed by maintenance immunotherapy suggest that biochemotherapy may still have a role as a “bridge to immunotherapy” in some patients with rapidly progressive disease. Given the low number of patients achieving durable benefit with cytokine-based immunotherapy, considerable recent effort has focused on identifying predictors of therapeutic response. Investigations suggest that immune responsiveness may be predetermined by a tumor microenvironment conducive to immune recognition and the host propensity to develop autoimmunity. Efforts to understand and further define pretreatment predictors of response through the use of gene expression and proteomic techniques are ongoing and raise the potential for eventually limiting cytokine-based immunotherapy to those most likely to benefit.

The outlook for patients with advanced melanoma remains bleak. Patients with stage IV melanoma have a median survival of 6 to 9 months, with 5-year survival rates of only 1% to 2%. An estimated 8,000 Americans will die of melanoma in 2005. Many of these patients are young (median age, ~50 years) and otherwise healthy; therefore, their loss represents a societal burden in excess of their actual numbers. In fact, although melanoma is the ninth most common cancer in the United States, it ranks second among solid tumors in terms of years of productive life lost. Common treatment approaches have included cytotoxic chemotherapy, cytokine-based immunotherapy, and combinations of chemotherapy and immunotherapy, the so-called biochemotherapy. This article reviews the current status of cytokine-based immunotherapy for advanced melanoma, including interleukin (IL)-2-based biochemotherapy.

Several cytokines, including IFNα and IFNγ, granulocyte macrophage colony-stimulating factor, and IL-2, IL-4, IL-6, IL-12, and IL-18 have been investigated in patients with advanced melanoma. The biological properties and relative antitumor effects of these various agents are displayed in Table 1. The best results to date have been observed with high-dose bolus IL-2. High-dose IL-2 administered at 600,000 to 720,000 units/kg by bolus i.v. infusion every 8 hours on days 1 to 5 and 15 to 19 received Food and Drug Administration approval for the treatment of patients with unresectable metastatic melanoma in January 1998. This approval was based on the ability of this IL-2 regimen to produce durable responses in a meaningful proportion of patients. Tumor responses were documented in 16% of patients, with 6% achieving a complete response (1). At the last, full analysis of the 270 patients presented originally to the Food and Drug Administration, the median duration of response for complete responders had yet to be reached but exceeded 59 months, and disease progression was not observed in any patient responding for longer than 30 months (2). Median survival for the entire group was 11.4 months, and with a minimum follow-up exceeding 5 years, 28 patients (10%) were confirmed to be alive, including 12 who were continuously disease or progression-free. A recent update through 2004 of this data set confirms the durability of responses, with no
relapses being observed in responding patients during the past decade (Fig. 1). These long-term follow-up data strongly suggest that some patients with advanced melanoma may actually be cured with high-dose IL-2 therapy.

Unfortunately, the toxic effects associated with the high-dose IL-2 treatment regimen have limited its use to selected patients with excellent organ function treated by experienced clinicians at well-established treatment centers. Efforts to develop more tolerable and/or effective IL-2–based treatment regimens either by long-term administration of lower doses or through combination of IL-2 with other cytokines such as IFNα, monoclonal antibodies, or various toxicity reduction agents have yet to produce results superior to high-dose IL-2 alone (3).

More recent efforts have focused on the combination of IL-2 with peptide vaccines. The combination of high-dose IL-2 and a mutated version of a HLA-A2–restricted GP100 peptide antigen (gp100-209-2M) produced tumor responses in >40% of patients treated at the National Cancer Institute Surgery Branch (4). In an effort to confirm the activity of this combination, the Cytokine Working Group recently completed a randomized phase 2 trial in which the gp100 vaccine was combined with three different high-dose IL-2 schedules (5). In this protocol, all patients received the gp100 209-2M vaccine on weeks 1, 4, 7, and 10 and were randomly assigned to receive high-dose IL-2 at the standard schedule (600,000 IU/kg, every 8 hours for 14 doses) on weeks 1 and 3 (arm 1); 7 and 9 (arm 2); or 1, 4, 7, and 10 (arm 3) of a 12-week cycle (Fig. 2). One hundred thirty-one patients were enrolled with follow-up data available on 116. Of these 116 patients, 14, including 12 from arm 2, did not receive any IL-2 due to early disease progression. Of these 116 patients, 17 (14.5%) exhibited a major tumor response (10 complete and 7 partial responses), including 19% from arm 1, 12.5% from arm 2, and 8.8% from arm 3. Despite extensive analysis of pretreatment and week 12 lymphocyte specimens, no correlation between overall immune function or specific immunoactivity against the gp100 peptide and clinical benefit was observed. Although median survival for the entire population exceeded 14 months, an impressive number for a multi-institutional trial, the tumor response rates suggested that the addition of the gp100 peptide failed to significantly enhance the antitumor activity of high-dose IL-2. Although this result is disappointing, formal evaluation of the efficacy of this combination and its effect on other measures of benefit, including time to progression and survival, must await the completion of the ongoing phase 3 trial comparing high-dose IL-2 with or without the gp100 peptide vaccine.

Recent investigations have shed light on possible limitations of IL-2–based immunotherapy. Signaling through the high-affinity IL-2 receptor has been shown to be critical for CD4+ CD25+ regulatory T-cell differentiation and survival in vivo. Several investigators have shown increased numbers of Tregs in patients with cancer relative to healthy donors. Furthermore, Cesana et al. (6) have recently reported an overall increase in Treg activation and frequency during IL-2–based immunotherapy, suggesting that in some patients IL-2 may lead to immune tolerance rather than antitumor immunity. Although only limited data were available, complete response was associated with a reduction of the Tregs back to normal levels in two of three patients. Efforts to shift the immune balance following IL-2 therapy in favor of immune activation rather than immune suppression have included administration of IL-2 following lymphodepletion (7), denileukin diftitox (CD25 immunotoxin), or CTLA4 antibody. Formal investigations of these approaches are currently ongoing.

Another approach to circumvent the immunomodulatory effects of IL-2 has been to test cytokines that may be more purely immunostimulatory. Although clinical trials that involve IL-4 and IL-6 have been disappointing, investigations with IL-12 and IL-18 have been more promising (8). IL-12 produced tumor responses in early phase 1 trials, including a complete remission in one patient treated at the top dose level (9). A peculiar schedule dependency associated with IL-12, in which

### Table 1. Cytokine therapy for melanoma, 2005

<table>
<thead>
<tr>
<th>Cytokine</th>
<th>Proposed mechanisms of action</th>
<th>Activity</th>
<th>Relative toxicity</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFNα</td>
<td>Immunoaugmentative, tumor Ag presentation, antiproliferative, antiangiogenic</td>
<td>10-15% RR, mostly small volume disease</td>
<td>2+</td>
<td>FDA-approved for adjuvant therapy in patients with stage II and III disease</td>
</tr>
<tr>
<td>IL-2</td>
<td>Expand and activate specific T cells</td>
<td>15% RR for high-dose regimen; durable responses, including some patients with visceral metastases</td>
<td>4+</td>
<td>FDA-approved for stage IV melanoma</td>
</tr>
<tr>
<td>GM-CSF</td>
<td>DC activation</td>
<td>Delays recurrence?</td>
<td>1+</td>
<td>In phase 3 investigations in adjuvant setting</td>
</tr>
<tr>
<td>IL-4</td>
<td>Proliferation of activated T cells</td>
<td>Inactive</td>
<td>2+</td>
<td>No current investigations</td>
</tr>
<tr>
<td>IL-6</td>
<td>Proinflammatory</td>
<td>Inactive</td>
<td>2+</td>
<td>No current investigations</td>
</tr>
<tr>
<td>IL-12</td>
<td>Th1 shift, IFNγ induction, antiangiogenic</td>
<td>Some activity combined with low-dose IL-2</td>
<td>2+</td>
<td>No current investigations</td>
</tr>
<tr>
<td>IL-18</td>
<td>IFNγ induction, Fas and T-cell-dependent killing, T-cell memory, antiangiogenic</td>
<td>Some responses in phase 1 and 2 trials</td>
<td>1+</td>
<td>Phase 2 studies in melanoma ongoing</td>
</tr>
</tbody>
</table>

Abbreviations: GM-CSF, granulocyte-macrophage colony-stimulating factor; RR, response rate; Ag, antigen; DC, dendritic cells; FDA, Food and Drug Administration.
a single “test dose” increased tolerance to subsequent therapy and possibly reduced antitumor effects, complicated the clinical development of this agent (10). Novel schedules of IL-12 were developed in an effort to sustain its biological activity. These studies have shown a correlation with the ability to sustain IFN-γ production and antitumor effects (11). The addition of low-dose IL-2 to IL-12 was able to sustain IFN-γ production in response to IL-12 in most patients and produced modest antitumor effects in some patients (12); however, the unavailability of IL-12 has prevented the performance of phase 2 investigations with this combination. In phase 1 studies, IL-18 has been shown to be well tolerated, and several patients have maintained stable disease through six cycles. Phase 2 studies of IL-18 in melanoma and phase 1 studies of other promising cytokines, including IL-15 and IL-21, are just under way.

An extensive evaluation of the combination of IL-2–based immunotherapy with cisplatin-based cytotoxic chemotherapy, so-called biochemotherapy, has been undertaken during the past decade. The results from multiple phase 2 trials taken in aggregate indicate that biochemotherapy produced responses in ~50% of patients, with 10% achieving unmaintained durable complete responses (13). Subsequent protocol modifications produced treatment regimens that seemed to maintain antitumor activity, yet were sufficiently well tolerated to enable more widespread inpatient or even outpatient use (14, 15). However, the superiority of such biochemotherapy regimens to either IL-2–based immunotherapy alone or cytotoxic chemotherapy remains to be proven. Early phase 3 trials produced mixed results. In a multicenter European phase 3 trial that compared biochemotherapy to an IL-2 and IFN combination, the biochemotherapy regimen produced a higher response rate, but the responses were of shorter duration such that no overall survival advantage or increase in the percentage of durable complete responders was observed (16). A second trial conducted at the National Cancer Institute Surgery Branch examined the activity of cisplatin, dacarbazine, and tamoxifen–based chemotherapy with or without high-dose IL-2. Although this study also showed more tumor responses in patients receiving the biochemotherapy combination, tumor responses were of short duration in each treatment group. Hence, this improved response rate did not translate into an improvement in either the number of durable complete responses or overall survival for the biochemotherapy-treated patients (17).

Another trial done at the M.D. Anderson Cancer Center evaluated a sequential biochemotherapy regimen that involved cisplatin, vinblastine, and dacarbazine (CVD), continuous infusion IL-2, and IFNα to CVD alone (18). One hundred ninety patients were enrolled and evenly divided between the two treatment arms. The response rate was 48% for the biochemotherapy arm and 25% for the CVD alone arm ($P = .001$). Median time to progression was also significantly longer with the biochemotherapy (4.6 versus 2.4 months), whereas the median survival difference was of borderline significance. Although this single institution data were promising, the regimen seemed too rigorous and toxic for more widespread investigation.

Questions concerning the value of biochemotherapy have been settled more definitively by the intergroup trial (E3695) that compared concurrent CVD plus IL-2 and IFN to CVD alone. Preliminary analysis of this study reported statistically insignificant improvements in response rate and time to progression favoring the biochemotherapy arm, but no overall survival advantage (19). In addition, the biochemotherapy arm was associated with significantly more toxicity, especially grade 3 and 4 toxic effects, and required more dose modifications. Based on the sum of these results, it must be concluded that biochemotherapy offers no significant advantage over either cytotoxic chemotherapy or IL-2–based immunotherapy and thus should not be considered as standard therapy for patients with stage IV melanoma.

Recent investigations with biochemotherapy have included efforts to reduce the high incidence of central nervous system relapse by substituting temozolomide for dacarbazine (20) and incorporating prophylactic cranial irradiation, minimizing the effect of tumor resistance and immune suppression by administering biochemotherapy in the adjuvant setting to patients with stage III B and III C disease and enhancing the durability of response by adding maintenance immunotherapy following

Fig. 1. Response duration curves for the 37 responding patients in the 270 patient cohort of high-dose IL-2–treated patients with advanced melanoma presented to the Food and Drug Administration in 1997. These curves are updated through 2004 and show a minimum follow-up of $>10$ years. As can be seen, the median duration of response for complete responders has not been reached, and no patient with tumor response at 30 months has subsequently exhibited disease progression.

Fig. 2. Treatment design for the Cytokine Working Group randomized phase 2 trial of the gp100 (209-2M) peptide vaccine in combination with three different high-dose IL-2 administration schedules.
maximal tumor regression (21). A recently completed multi-institutional trial of maintenance granulocyte macrophage colony-stimulating factor and IL-2 immunotherapy following biochemotherapy reported encouraging results with a 44% response rate, 9-month median time to progression, and 14-month median overall survival (22). Although a large confirmatory cooperative group trial of this approach seems unlikely, these data suggest that biochemotherapy may still have a role as a “bridge to immunotherapy” in some patients with rapidly progressive disease.

Given the low number of patients achieving durable benefit and the high level of toxicity associated with IL-2–based therapy, considerable recent effort has focused on identifying predictors of therapeutic response. A retrospective analysis of 374 patients treated with high-dose IL-2 between 1988 and 1999 revealed a correlation between sites of metastatic disease and objective response rate (54% for patients with cutaneous or subcutaneous metastasis compared with 12% for disease at other sites; ref. 23). Other analyses correlated response with Cw7 phenotype, development of vitiligo, autoimmune thyroid dysfunction, or low pretreatment serum levels of C-reactive protein or IL-6 (24). The association of clinical benefit from cytokine-based therapy and autoimmune phenomenon has also recently been reported for the use of IFNα in the adjuvant setting (25) and for CTLA4 antibody administration (26), suggesting that benefit from cytokine-based therapy may be limited to patients capable of mounting an immune response to self-antigens. This may explain that failure of cytokine-based therapy to produce benefit in >15% of patients and may help to identify a population of patients who might be the focus of such cytokine treatments.

More recent studies have examined pretreatment gene expression profiles within subcutaneous tumor and correlated results with treatment outcome. Tumor response was associated with expression of genes related to T-cell regulation, suggesting that immune responsiveness might be predetermined by a tumor microenvironment conducive to immune recognition (27). In addition, response to biochemotherapy has been reported to potentially correlate inversely to levels of methylated tumor-associated DNA in the peripheral blood (28). Efforts to confirm and refine these response correlates and to identify additional and reproducible pretreatment predictors of response through the further use of gene expression and proteomic techniques and the assessment of tumor-associated epigenetic modifications within either the peripheral blood or tumor itself are ongoing and raise the potential of eventually limiting this toxic therapy to those most likely to benefit.

In conclusion, few if any effective therapies exist for patients with stage IV melanoma. Although high-dose IL-2 can offer some benefit to a subset of patients, it comes at a significant cost in terms of toxic effects and expense. Currently, no benefit has been established for the addition of any other therapy to high-dose IL-2. Of concern, recent observations suggest that IL-2–based immunotherapy may produce immune suppression in many patients and that those who benefit might be limited to the small percentage of patients able to mount immune responses against self-antigens. Although cytokine therapy is currently of limited benefit, it is likely to remain a critical component of all curative treatment strategies for patients with advanced melanoma. Opportunities for enhancing cytokine-based therapy include better patient selection, elimination of immunosuppressive effects, and targeting cytokines directly to the tumor sites. Given the critical need to enhance our understanding of the mechanisms underlying response and resistance to cytokine-based immunotherapy, whenever possible, patients should be considered for enrollment in research protocols addressing these issues.

Open Discussion

Dr. Hwu: High-dose IL-2 was approved because some patients are essentially cured with long-term disease-free intervals. However, in your update, it looked like both the chemotherapy and biochemotherapy arms responded. Is it possible that these are all the same patients?

Dr. Atkins: In any stage IV melanoma trial, there is survival somewhere between 5% and 10%. Patients with either cutaneous or nodal disease may even be misdiagnosed as stage IV and then get treatment. After treatment, they have some response and may have their residual disease resected. Some of those patients may also have received other therapies besides biochemotherapy. It’s possible that people in the chemotherapy arm went on to receive and respond to IL-2, for example.

Dr. Sosman: When you look at the progression-free survival, there are virtually no progression-free patients at the end of the curve.

Dr. Atkins: Some patients haven’t progressed. But if you look at responders to biochemotherapy, in the initial studies done at M.D. Anderson and other places, 60% of the patients with complete remission remain disease-free in the long term; there were no relapses after 2 years. We’re not seeing that with the concurrent biochemotherapy trials.

Dr. Sondak: There was originally a question about whether the increased prevalence of IFN pretreatment might affect the results in the E3695 trial. Do you have any data on that?

Dr. Atkins: There was a slight improvement in time to progression in patients who hadn’t had prior IFN versus those who had had prior IFN, which completely reproduced what our original goals were for a time-to-progression end point. However, there was no difference in response rates or survival.

Dr. Weinstock: There has been a lot of discussion about timing of biotherapy versus chemotherapy. Some people were fixed on how critical it is to have one before the other, and other people said to have both at the same time. Are you satisfied that this issue is resolved and that it doesn’t matter which is first?

Dr. Atkins: I’m not satisfied that it’s completely resolved, but we can’t answer every question that we want to have answered in oncology. We have to prioritize the questions that we try to answer.

Dr. Kirkwood: You’ve suggested that the data for IL-2 vis-à-vis specific immune responses that can be tracked during therapy has only been associated with a depression of the measurable end points.

Dr. Atkins: I didn’t present that data. The analysis we did of the IL-2 + peptide study was done in samples obtained at 12 weeks. There would have been plenty of time for the immune system to recover from the effects of IL-2. The only thing that might have been a consistent effect was that there were more T-regulatory cells at 12 weeks than pretreatment, and it didn’t seem to make a difference with responders or not.
Dr. Kirkwood: In the context of relevant outcome, can we draw any conclusions from our experience regarding the role of IL-2 and immune responses?

Dr. Gajewski: According to Franco Marincola’s gene array data in response to IL-2, perhaps it’s the constellation of all of these cytokines that are induced secondarily by the IL-2 that is activating some nonadaptive immune cell compartment (such as macrophages) to cause tumor regression.

Dr. Hwu: That may be the missing component that distinguishes why tumors look different than viruses. When you have a viral infection, you get a lot of inflammation at the virus site so that T cells know how to come back to the infected site.

Dr. Atkins: Maybe we need to do a neoadjuvant trial to sort this out.

Dr. Sosman: It would be hard to sell any kind of biochemotherapy study in melanoma at this time. There are some big scientific issues that would need to be dealt with for review committees to support a trial including biochemotherapy.

Dr. Gajewski: You could come up with at least some theoretical reasons why this regimen was not superior to chemotherapy alone that would justify phase 2 trials to address some of those individual concerns. For example, granulocyte colony-stimulating factor, which has been suggested to bias against a T_{H1} cytokine profile, may be counterproductive. In addition, the use of three chemotherapy drugs, including vinblastine that induces more myelosuppression, might not allow dose intensity, and thus may facilitate toxicity but probably doesn’t add anything to clinical response.

Dr. Sosman: If the premise is that combination chemotherapy isn’t much better than single agent, why not look at dacarbazine followed by IL-2 and granulocyte-macrophage colony-stimulating factor in his way?

Dr. Atkins: That would be reasonable. The only issue would be whether you can gain enough control of the disease with the dacarbazine alone or whether you are left with most of your patients having more disease by the time immunotherapy is initiated. Some of this information will be useful for when we have better ways of controlling the disease.

Dr. Haluska: There seems to be an artificial dichotomy between the genetic understanding and the immunologic understanding and responses. There are a couple of thought experiments that we can do. One experiment is the responsive-ness of skin-only disease to high-dose IL-2 therapy. Skin-only disease is eminently curable with chemotherapy; with limb perfusion, the response rates are 80% and the complete response rates are 40%. We have to think about what genetically controls the response of all cells to immune killing. That final common pathway is probably similar for cytotoxic and granzyme/perforin B-mediated pathways. As we come to understand response to immunotherapy and chemotherapy, there are probably some commonalities that will emerge from those genetic studies.

Dr. Atkins: I don’t think that the same populations are responding to these agents. It’s even more complicated than you have just posed.

Dr. Kirkwood: I agree. The IL-2 response is 15% after failure of biochemotherapy. There is also little cross-resistance to IFN with IL-2.

Dr. yardım: None of that contradicts the concept that there is a final common pathway that you can activate in a percentage of melanomas.

Dr. Haluska: We focus heavily on resistance to therapy, but in fact cancer is extraordinarily susceptible to the therapies that we give. High-dose IL-2 will kill all melanomas in 6% of patients. If you look at melanocytes as being a positive control, if the target is equally expressed on melanocytes and cancer cells, you’d expect, unless there was a genetic difference in how those cells respond, that they’d be equally affected, and they’re not. We can’t even explain the patchy distribution of vitiligo we see. What sets apart melanocyte A on your forearm versus melanocyte B on your inner arm? There is something that makes cancer cells susceptible in a subpopulation, whereas their normal counter parts aren’t, and we don’t understand that.

References


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