Practical Guidelines for the Management of Biochemotherapy-related Toxicity in Melanoma

Antonio C. Buzaid and Michael Atkins

Abstract

The combination of cisplatin-based chemotherapy with interleukin 2 (IL-2) and IFN-α, referred to as biochemotherapy or chemioimmunotherapy, has shown promising antitumor activity in patients with metastatic melanoma. Phase II studies have reported overall response rates ranging from 40 to 60%, with durable complete remissions in ~10% of the patients. Toxicity, however, is often severe and can be life-threatening if the healthcare team is not familiar with toxicity management. In this report, we briefly describe the clinical results of the most effective biochemotherapy regimens and provide a detailed description and management of the most common toxic effects, with emphasis on the concurrent biochemotherapy program initially developed at M. D. Anderson Cancer Center and currently being tested in a slightly modified version in two large-scale Intergroup Phase III trials.

Introduction

Cutaneous malignant melanoma is an increasingly common clinical problem. Estimates indicate that in 2000 a total of 44,700 new cases of melanoma will be diagnosed in the United States (1). Of all cases of melanoma diagnosed, ~20% will eventually die secondary to metastatic disease. The treatment of metastatic melanoma remains unsatisfactory, with patient survival dictated primarily by the pace of the disease (2). Chemotherapy when used alone produces responses in approximately 10–30% of the patients, but durable remissions are rare, occurring in <2% of patients (2). Immunotherapy with high dose IL-2 has shown promise with overall responses in 16–20% of patients, with durable remissions in 4–6% of patients (3, 4). This treatment has been associated with significant toxicity, however, limiting its use to young patients with excellent organ function treated at a few select treatment centers. Lower dose IL-2 regimens, IFN-α, combinations of IL-2 and IFN-α, or other immunotherapy approaches have generally produced lower response rates and few durable remissions (5).

Biochemotherapy

Phase II Studies

The limited results observed with chemotherapy and immunotherapy when used alone have led many investigators to empirically combine chemotherapy drugs with immunotherapy agents (2). Of all of the currently used treatment modalities for metastatic melanoma, cisplatin-based regimens combined with biological agents such as IFN-α and IL-2, referred to as “biochemotherapy” or “chemioimmunotherapy,” appear to have attained the highest response rates (2). Phase II studies have shown overall response rates ranging from 40 to 60% with CR rates on the order of 10–20% (6–16). Durable remissions exceeding 5 years were seen in ~10% of the patients, and relapses beyond the 2-year time point were distinctly uncommon, thus suggesting that these patients exhibiting durable responses were likely to be “cured” (6, 8–10). The results of these Phase II studies are shown in Table 1. Meta-analyses suggested improved response rates and possibly survival for combinations involving cisplatin, IL-2, and IFN-α relative to either chemotherapy or immunotherapy alone. In one analysis involving 631 patients, biochemotherapy regimens produced a response rate of 45% compared to 21 and 15% with IL-2 and IFN-α or IL-2 alone, respectively. Median survival, however, was not significantly different between the groups (10.5 months) with 20 and 10% survival rates at 2 and 5 years, respectively (17). Another meta-analysis analyzed 154 studies involving over 7000 patients. The highest response rate of 47% and median survival of 10 months were observed in patients who received cisplatin, DTIC, IL-2, and IFN-α (18).

Many of these early biochemotherapy regimens involved extensive inpatient treatment and substantial toxicity, expense, and time commitment. A number of investigators have endeavored to devise regimens with toxicity acceptable for more widespread use while retaining roughly comparable antitumor activity. These efforts have included the use of s.c. IL-2 or the concurrent administration of the biotherapy and chemotherapy components. Unfortunately, biochemotherapy regimens involving s.c. IL-2 administration appeared to produce lower response rates than were generally seen with regimens involving i.v. IL-2. For example, the Cytokine Working Group performed a randomized Phase II trial of two outpatient biochemotherapy regimens involving DTIC, cisplatin, and IFN-α with IL-2 administered either i.v. or s.c. (16). There were 16 responses including 5 CRs in the 44 patients who received the i.v. IL-2 regimen (response rate, 36%), whereas there were only 6 responses (including 1 CR) in the 36 patients assigned to receive the s.c. IL-2 regimen (response rate, 17%; Ref. 16). In addition, a study in which patients were randomly assigned to receive either the Dartmouth regimen or the Dartmouth regimen preceded by IL-2 administered by the s.c. route (days −2 to 0) and followed by...
IFN-α (days 1–3) showed no difference in response rate (22% for the biochemotherapy versus 27% for the Dartmouth regimen), median duration of response (2.8 versus 2.5 months), or survival (5 versus 5.5 months; Ref. 19). The lower overall response rates for the biochemotherapy regimens involving s.c. IL-2 in these two studies relative to the i.v. IL-2 biochemotherapy regimens mentioned previously suggest a potential schedule, dose, and route of administration effect for the IL-2 in biochemotherapy combinations.

By contrast, concurrent biochemotherapy regimens appeared to have to be less complex and toxic while maintaining antitumor activity comparable to other regimens. One such regimen, developed at M. D. Anderson Cancer Center, involved CVD chemotherapy administered concurrently with IL-2 and IFN-α for a maximum of six cycles. Tumor responses were observed in 34 of 53 patients (64%), with 20% complete responses and 9% durable CRs (9). In another study, this regimen was modified in an effort to reduce toxicity. Modifications included antibiotic and G-CSF prophylaxis, prohibition of long-term central venous access, and restriction to a maximum of four cycles of therapy. Tumor responses were seen in 19 of 40 evaluable patients (response rate, 48%) including 8 CRs (12). In other studies, the preliminary results of a Phase III study conducted at the National Cancer Institute. Patients were randomized to receive cisplatin, DTIC, and tamoxifen or cisplatin, DTIC, and tamoxifen followed by IL-2 plus IFN-α. In 52 patients treated with chemotherapy alone, there were 14 objective responses (27%) including 4 CRs. In 50 patients treated with biochemotherapy, there were 22 objective responses (44%; \( P = 0.071 \)), including 3 CRs. There was a trend toward a survival advantage for patients receiving the chemotherapy alone (\( P = 0.052 \); median survival of 15.8 months compared with 10.7 months). This unusual survival finding is most likely attributable to either the administration of high dose IL-2 as salvage therapy to patients failing to respond to chemotherapy or imbalances between the treatment arms that can be seen with such small numbers of patients.

More recently, Eton et al. (23) reported the preliminary results of the M. D. Anderson Cancer Center randomized study comparing sequential biochemotherapy with chemotherapy alone. A total of 190 patients were enrolled into the study, and of these, 91 were evaluable in the biochemotherapy arm and 92 in the CVD arm. The overall response rate was 48% for the biochemotherapy arm versus 25% for the CVD arm (\( P = 0.001 \)) with 6 CRs in the biochemotherapy arm and 1 in the chemotherapy arm. The median time to progression was 4.6 months, and the median survival was 11.8 months for the biochemotherapy arm versus 2.4 months and 9.5 months for the chemotherapy arm (\( P = 0.0007 \) for time to progression and \( P = 0.055 \) for overall survival). The definite determination of the value of biochemotherapy relative to chemotherapy alone must await the completion of the United States Intergroup trial comparing a modified version of the concurrent biochemotherapy regimen (12) to CVD chemotherapy alone.

### Table 1

<table>
<thead>
<tr>
<th>Study</th>
<th>Regimen</th>
<th>n</th>
<th>% CR</th>
<th>% PR</th>
<th>% OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>i.v. IL-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Richards et al. (6)</td>
<td>Sequential CBDT/BIO(^a)</td>
<td>83</td>
<td>15</td>
<td>40</td>
<td>55</td>
</tr>
<tr>
<td>Antoine et al. (7)</td>
<td>Sequential C/IL-2/IFN-α</td>
<td>129</td>
<td>10</td>
<td>39</td>
<td>49</td>
</tr>
<tr>
<td>Flaherty et al. (16)</td>
<td>Sequential CD/IL-2/IFN-α(^b)</td>
<td>43</td>
<td>12</td>
<td>25</td>
<td>37</td>
</tr>
<tr>
<td>Legha et al. (8, 9)</td>
<td>Sequential CVD/BIO(^b)</td>
<td>30</td>
<td>30</td>
<td>43</td>
<td>73</td>
</tr>
<tr>
<td></td>
<td>Sequential BIO/CVD(^b)</td>
<td>30</td>
<td>17</td>
<td>30</td>
<td>47</td>
</tr>
<tr>
<td></td>
<td>Concurrent CVD + BIO</td>
<td>52</td>
<td>21</td>
<td>43</td>
<td>64</td>
</tr>
<tr>
<td>O’Day et al. (10)</td>
<td>Concurrent CVD + BIO</td>
<td>45</td>
<td>23</td>
<td>34</td>
<td>57</td>
</tr>
<tr>
<td>McDermott et al. (12)</td>
<td>Concurrent CVD + BIO</td>
<td>44</td>
<td>20</td>
<td>28</td>
<td>48</td>
</tr>
<tr>
<td>Gibbs et al. (11)</td>
<td>Concurrent CVD + BIO</td>
<td>43</td>
<td>12</td>
<td>35</td>
<td>47</td>
</tr>
<tr>
<td>s.c. IL-2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ron et al. (13)</td>
<td>Carboplatin/DTIC/IL-2/IFN-α</td>
<td>16</td>
<td>0</td>
<td>38</td>
<td>38</td>
</tr>
<tr>
<td>Atzpodien et al. (14)</td>
<td>Carboplatin/DTIC/IL-2/IFN-α</td>
<td>40</td>
<td>7.5</td>
<td>27.5</td>
<td>35</td>
</tr>
<tr>
<td>Thompson et al. (15)</td>
<td>CBDT/IL-2/IFN-α</td>
<td>53</td>
<td>19</td>
<td>23</td>
<td>42</td>
</tr>
<tr>
<td>Johnston et al. (19)</td>
<td>CDBT/BIO(^b)</td>
<td>35</td>
<td>3</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>Flaherty et al. (16)</td>
<td>CD/IL-2/IFN-α(^b)</td>
<td>36</td>
<td>3</td>
<td>16</td>
<td>19</td>
</tr>
</tbody>
</table>

\(^a\) CBD, cisplatin/1,3-bis(2-chloroethyl)-1-nitrosourea/DTIC/tamoxifen; BIO, IFN-α + IL-2; OR, overall response; PR, partial response.

\(^b\) Randomized Phase II study.
The malaise increases because of the IL-2 and IFN-γ fever pattern is large. Fig. 1 shows an example of a fever curve.

The chills and fever are most intense in the first day and take place in general 3–40 °C. In the subsequent days, the fever will usually be less, and the chills become less marked, but the variability in the fever pattern is large. Fig. 1 shows an example of a fever curve. The malaise increases because of the IL-2 and IFN-γ cumulative effect, reaching its peak on day 5 or 6 and lasting well into the second week, especially in regimens that include week 2 outpatient IFN-γ administration. Patients start to feel better on the third week, i.e., 1 week prior to initiation of the subsequent cycle.

Management of Toxicity of Biochemotherapy

The most common side effects of biochemotherapy are shown in Table 3. Each toxicity will be described in detail, and practical guidelines concerning its management will be provided.

Constitutional Effects

Description. All patients treated with biochemotherapy will experience a flu-like syndrome that consists of fever, chills, myalgia, and malaise (9). The chills and fever are most intense in the first day and take place in general 3–6 h after the first IFN-γ injection. On the first day, the fever may reach as high as 39–40 °C. In the subsequent days, the fever will usually be less, and the chills become less marked, but the variability in the fever pattern is large. Fig. 1 shows an example of a fever curve. The malaise increases because of the IL-2 and IFN-γ cumulative effect, reaching its peak on day 5 or 6 and lasting well into the second week, especially in regimens that include week 2 outpatient IFN-γ administration. Patients start to feel better on the third week, i.e., 1 week prior to initiation of the subsequent cycle.

Management. The fever will occur despite the use of acetaminophen around the clock, although without acetaminophen the fever tends to be higher. In patients with fever exceeding 39°C, we prescribe a nonsteroidal anti-inflammatory agent (such as naproxen 375–500 mg p.o.) on an as-needed basis. Although some institutions administer nonsteroidal anti-inflammatory drugs at regular intervals from day 1, this must be done cautiously because of potential nephrotoxic effects. For rigors, we use meperidine 50–75 mg i.v. every 4 h, as needed. Significant fevers after day 3 of therapy should be presumed to be possibly infectious in nature. Blood from the patients should be pancultured, and if infection is considered possible, broad-spectrum antibiotics should be administered (see below).

Hematological Effects

Description. All patients will experience varying degrees of anemia, neutropenia, and thrombocytopenia (9). The hematological toxicity is cumulative. It is common to observe thrombocytopenia and leukopenia on day 5 that are largely attributable to the biotherapy component of the regimen and tend to resolve rapidly. Significant myelosuppression related to the chemotherapy component is observed during the second and third weeks of therapy. In the original M. D. Anderson studies, growth factors such as G-CSF or erythropoietin were not used routinely, and severe neutropenia and anemia were common events (9). For instance, with the concurrent biochemotherapy the hemoglobin level dropped 1–2 g/cycle, and transfusion was necessary in ~50% of the patients, including almost all patients receiving more than two cycles of therapy. Neutropenia grade 4 was observed in all patients, and platelet transfusion was re-

### Table 2 Phase III studies of biochemotherapy with chemotherapy or biotherapy alone

<table>
<thead>
<tr>
<th>Study and regimen</th>
<th>n</th>
<th>% CR</th>
<th>% PR*</th>
<th>% OR</th>
<th>TTP (mo)</th>
<th>OS (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosenberg et al. (22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDT/BIO</td>
<td>50</td>
<td>6</td>
<td>38</td>
<td>44</td>
<td>NR</td>
<td>10.7</td>
</tr>
<tr>
<td>CDT</td>
<td>52</td>
<td>8</td>
<td>19</td>
<td>27</td>
<td>NR</td>
<td>15.8</td>
</tr>
<tr>
<td>Keilholz et al. (20)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/BIO</td>
<td>60</td>
<td>5</td>
<td>28</td>
<td>33</td>
<td>3</td>
<td>9</td>
</tr>
<tr>
<td>BIO</td>
<td>66</td>
<td>6</td>
<td>12</td>
<td>18</td>
<td>1.7</td>
<td>9</td>
</tr>
<tr>
<td>Dorval et al. (21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C/BIO</td>
<td>52</td>
<td>4</td>
<td>21</td>
<td>25</td>
<td>9.1b</td>
<td>10.9</td>
</tr>
<tr>
<td>C/IL-2 alone</td>
<td>49</td>
<td>6</td>
<td>10</td>
<td>16</td>
<td>6.6b</td>
<td>10.4</td>
</tr>
<tr>
<td>Eton et al. (23)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD/BIO</td>
<td>91</td>
<td>6.5</td>
<td>41.5</td>
<td>48</td>
<td>4.6</td>
<td>11.8</td>
</tr>
<tr>
<td>CVD</td>
<td>92</td>
<td>1</td>
<td>24</td>
<td>25</td>
<td>2.4</td>
<td>9.5</td>
</tr>
</tbody>
</table>

* PR, partial response; C, cisplatin; D, DTIC; B, 1,3-bis(2-chloroethyl)-1-nitrosourea; T, tamoxifen; BIO, IL-2 plus IFN-γ; OR, overall response; TTP, time to progression; NR, not reported; OS, overall survival.

### Table 3 Most common toxic effects of biochemotherapy

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constitutional</td>
<td>Fever, chills, malaise, myalgia</td>
</tr>
<tr>
<td>Hematologic</td>
<td>Anemia, neutropenia, thrombocytopenia</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Anorexia, nausea, vomiting, diarrhea, elevation of liver function tests</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypotension, arrhythmias, congestive heart failure</td>
</tr>
<tr>
<td>Renal and electrolyte</td>
<td>Increased creatinine, hypomagnesemia, hyponatremia</td>
</tr>
<tr>
<td>Infection</td>
<td>Catheter-related, neutropenic fever, oral candidiasis</td>
</tr>
<tr>
<td>Cutaneous/mucosal</td>
<td>Skin rash, oral pharyngitis, alopecia, vitiligo</td>
</tr>
<tr>
<td>Endocrine</td>
<td>Hyper- and hypothyroidism</td>
</tr>
<tr>
<td>Neurologic</td>
<td>Peripheral neuropathy, depression, insomnia, latency, and cognitive changes</td>
</tr>
</tbody>
</table>

or April 3, 2017. © 2001 American Association for Cancer Research.
and continuing through the week 2 nadir and until the absolute
neutrophil count reaches >5,000/μl. In addition, erythropoietin
40,000 units s.c. weekly may also be started on day 6 of cycle
1. Patients experiencing grade 4 neutropenia (WBC <500/μl) or
thrombocytopenia (platelets <25,000/μl) should have their
doses of DTIC and vinblastine reduced by 25% in subsequent
treatment cycles.

Gastrointestinal Effects

Description. Anorexia, nausea, and vomiting occurs almost
universally in patients receiving biochemotherapy. Many
patients also experience diarrhea. Nausea and vomiting occur in
many patients despite the use of high-doses of 5HT3 receptor
antagonists (ondansetron and granisetron). Vomiting is typically
most severe on day 1, when DTIC is administered. Delayed
nausea and vomiting, lasting from 3 to 7 days after administra-
tion of cisplatin, are also common. Higher doses of anti-5HT3
anti-emetics (e.g., 32 mg i.v. qd of ondansetron or 3 mg i.v. qd
of granisetron) greatly reduce the incidence of grade 3 nausea
and vomiting but clearly are not effective in all patients. The
biotherapy and the resultant inability to co-administer steroids
are likely responsible for the suboptimal control of the nausea
and vomiting, because anti-5HT3 agents usually prevent nausea
and vomiting induced by the chemotherapy alone.

Diarrhea usually does not start until day 4 and may con-
tinue until days 8–9 of the biochemotherapy regimen. It is
common to observe mild constipation in the first 3 days of the
biochemotherapy, probably induced by a combination of the
anti-5HT3 antagonists and the vinblastine. It is inadvisable,
however, to use laxatives to treat the constipation, because it is
usually transient and frequently followed by diarrhea induced by
the biotherapy. Anorexia is most severe during administration of
the therapy and lasts up to 1 week after its completion. Patients
may lose 2–3 kg/cycle of therapy. Liver function test abnor-
malities are, although common, less frequent and milder than those
typically seen with high-dose IL-2 or high-dose IFN-α regimens
(9, 25). Treatment modifications are usually unnecessary.

Management. In addition to using high-doses of 5HT3
antagonists, we have routinely used a phenothiazine or a buty-
rophenone, such as perchlorperazine 10 mg i.v. every 6–8 h or
droperidol 2.5 mg i.v. every 6–8 h around the clock, particularly
on days 1 and 2 when nausea and vomiting are usually more
intense. We continue the use of the phenothiazine or butyro-
phenone in patients in which nausea persists after day 2 and change
to as needed in those that tolerate therapy better. To reduce the
appearance of extrapyramidal side effects and possibly enhance
the anti-emetic protection, we routinely add diphenhydramine
i.v. and/or lorazepam 0.5–1.0 mg p.o. or i.v. prior to each dose
of the phenothiazine or butyrophenone. Although this regimen
produces somnolence, it is highly effective in controlling nausea
and vomiting in most patients. On a PRN basis, we prescribe
additional doses of the phenothiazine or the butyrophenone with
diphenhydramine. We do not recommend the use of high-doses
of metoclopramide (≥1 mg/kg/dose), because this often pro-
duces diarrhea, which is already common with biochemo-
therapy. Lower doses (e.g., 10–20 mg i.v. every 6 h), however,
my be useful in some patients. In patients with refractory nausea
and vomiting despite the above measures, we have used tetra-
hydrocannabinol in doses of 5 mg every 6 h ATC. Steroids are
prohibited, because they will interfere with the immune activa-
tion produced by the biotherapy.

Delayed nausea is best managed with aggressive i.v. hy-
dration, i.v. 5HT3 antagonists, and combinations of the addi-
tional drugs mentioned above. Once again, steroids are prohib-
ited. Patients exhibiting vomiting after day 3 of each cycle are
at risk for delayed nausea and vomiting. They should only be
discharged if nausea is controlled and the patient is taking p.o.
fluids without vomiting. Despite the above measures, patients
with persistent vomiting during week 2 of a cycle should have
their week 2 IFN-α doses held (if prescribed as in the Intergroup
study), and consideration should be given to a 25% reduction in
cisplatin dose during their subsequent cycles of therapy.

Diarrhea can usually be managed with loperamide 4 mg
every 4–6 h PRN. Patients with persistent diarrhea, despite the
above measures, should be evaluated for a secondary cause,
such as Clostridium difficile infection.

During the first 2 weeks of a 3-week biochemotherapy
schedule, patients frequently have difficulties with oral intake. In
patients that develop severe anorexia, we suggest either tetra-
hydrocannabinol 2.5 mg p.o. every morning or megestrol acetate
800 mg p.o. every day after the hospital discharge.

Cardiovascular Effects

Description. The most common cardiovascular toxicities
are hypotension and capillary leak syndrome. These occur be-
cause of the release of nitric oxide from the endothelial cells,
producing vasodilation and increased permeability of the blood
vessels (26). Unlike the high-dose IL-2 regimens where hypo-
tension can be severe, often requiring management in the inten-
sive care unit, with the concurrent biochemotherapy program
hypotension is usually mild to moderate and easily manageable.

Fig. 1  Fever profile of concurrent biochemotherapy.
in a general hospital ward (9). In our experience, mild hypotension managed with i.v. fluids occurs only in about one-half of the patients, whereas moderate hypotension requiring pressors occurs in 10–40% of the patients (9, 12). Capillary leak is universal, and some fluid retention is even desirable to maintain renal perfusion. Peripheral edema and weight gain, in general between 5 and 10 kg, is common.

Some patients may experience mild dyspnea and exhibit rales on both lung bases, but severe dyspnea, congestive heart failure, or even noncardiogenic pulmonary edema is rare with the concurrent biochemotherapy regimens. Once IL-2 is finished, the patients start to have a brisk diuresis, and their weight returns to baseline within 5 days after completion of the IL-2 infusion (9). Diuretics are unnecessary unless the patient is experiencing dyspnea. Occasional patients may develop cardiac arrhythmias, most commonly atrial fibrillation (9). This is more common in patients with a history of atrial arrhythmias and those requiring dopamine. The cardiac toxicities such as myocarditis or myocardial ischemia are uncommon (9).

**Management.** Patients should discontinue any antihypertensive therapy at least 24 h prior to initiating each cycle of biochemotherapy. Blood pressure should be checked every 4 h during IL-2 therapy. Patients experiencing hypotension should have their blood pressure checked at a minimum of every 2 h. Target minimum systolic blood pressure should be 85 mm Hg for patients <40 years of age with no cardiac problems and 90 mm Hg for the remainder of the patients. Patients experiencing a fall in systolic blood pressure below their established target should be managed with a fluid bolus of NS 500 ml i.v. over 30 min and an increase in the rate of the maintenance i.v. fluids, usually from 100 ml/h to 150 ml/h. There is no major advantage for using a colloid such as albumin in this setting (27). If the patient does not respond to these measures, then the IL-2 infusion should be interrupted and dopamine at 3 \( \mu g/kg/min \) should be started and the dose titrated to keep systolic blood pressure above the patient’s target. If \( >6 \mu g/kg/min \) of dopamine is required to maintain systolic blood pressure, then phenylephrine should be added, beginning at 0.2 \( \mu g/kg/min \) and titrated up as necessary to maintain blood pressure. It is, however, extremely rare to need to use phenylephrine with the concurrent biochemotherapy regimen, and sepsis should be strongly considered in this setting.

Although during the M. D. Anderson studies IL-2 was not discontinued in the event of hypotension requiring pressors, the approach we currently recommend follows the Intergroup guidelines, which are more conservative. IFN-\( \alpha \), cisplatin, and vinblastine should also be held while patients are receiving blood pressure support. When the systolic blood pressure no longer requires dopamine support, IL-2 and IFN-\( \alpha \) can be resumed at 50% dose reduction. Missed time of the IL-2 infusion should not be made up. Missed IFN-\( \alpha \), cisplatin, or vinblastine can be given if hypotension resolves within 6 h of scheduled dosing; otherwise, they should be omitted for that treatment day. Hypotension becomes more severe with successive cycles of therapy. Patients experiencing a second episode of hypotension requiring pressor support, despite a 50% reduction in IL-2 and IFN-\( \alpha \), should have the biotherapy held for remaining cycles.

As stressed previously, a critical element in the differential diagnosis of hypotension during IL-2 therapy is sepsis. It is important to emphasize that in the initial biochemotherapy studies, there were \( \sim 1\% \) deaths because of unrecognized sepsis. Because it is difficult to clinically distinguish between sepsis and IL-2 toxicity, in the event of severe hypotension, we favor that the patient’s blood be pancultured and the patient empirically started on broad-spectrum antibiotics (see “Infection” section for details).

Patients experiencing dyspnea associated with blood oxygen desaturation (<92% \( O_2 \) saturation) should have all therapy held. The major differential diagnosis for dyspnea is IL-2-induced pulmonary edema, infection, and congestive heart failure. In this setting, a chest-X-ray should be ordered, and diuretics or antibiotics should be used on an as-needed basis. In patients that are more susceptible to capillary leak and dyspnea (for instance because of a diastolic myocardial dysfunction), we have successfully used mannitol 40 g i.v. over 1 h every 8 or 12 h ATC to avoid excessive positive fluid balance.

**Renal and Electrolyte Disorders**

**Description.** Significant elevations in serum creatinine occur in about 5–10% of the patients receiving biochemotherapy. Although creatinine elevation during high-dose IL-2 alone therapy is not of great concern because it is primarily pre-renal and rapidly reversible (28), elevations of serum creatinine \( >1.6 \) mg/dl during concurrent biochemotherapy requires immediate attention. In particular, cisplatin should be held because of it potential to produce acute tubular necrosis in this setting. Although in most instances creatinine elevations quickly resolve after discontinuation of the IL-2, the administration of cisplatin in the setting of an IL-2 induced pre-renal state and can lead to prolonged nephrotoxicity. In the M. D. Anderson Phase II experience with concurrent biochemotherapy, 6% of the 53 patients developed grade III and IV renal toxicity, and 1 patient had permanent renal failure (9) while in the modified concurrent biochemotherapy regimen; significant nephrotoxicity was rare, with only 6 patients requiring a modification in cisplatin dosing (12).

Mild hyponatremia is seen in almost all patients and is typically dilutional in nature. Moderate to severe hypomagnesemia, attributable to cisplatin-induced salt-wasting, is seen in about one-half of the patients and can be severe, leading to muscle weakness and even potentially life-threatening cardiac arrhythmias (8, 9). Hypomagnesemia becomes progressively worse with each successive cycle of therapy and therefore requires close monitoring (8, 9).

**Management.** It is imperative to maintain adequate urine output to reduce the possibility of acute renal failure. We recommend that patients have a urinary output \( \geq 100 \) ml/h; otherwise, some form of therapeutic intervention should be instituted. We strongly suggest that a standing order be written to contact the attending physician if the urine output is <800 ml/8-h shift. If this happens, we initially recommend NS bolus 500 ml i.v. over 30 min as well as an increase in the maintenance i.v. fluids rate from 125 to 150 ml/h. If these measures are not effective within 3 h, then one should consider starting low-dose dopamine at renal doses, i.e., 1–2 \( \mu g/kg/min \). Patients should have voided at least 500 ml in the 4 h before cisplatin administration. If adequate urine output cannot be maintained, then cisplatin should be held. Our experience suggests that dopamine is the most effective therapeutic strategy to enhance diuresis. This
recommendation is also supported by a randomized trial that showed that dopamine in renal doses reduced the incidence of renal failure in patients receiving IL-2 alone (29). If hydration alone is inadequate to induce urine flow at the time cisplatin is scheduled, then one could consider furosemide 20 mg i.v. push or mannitol 40 g i.v. over 30 min to stimulate diuresis. Proceed with cisplatin only when adequate urine output has been documented. Patients with serum creatinine >1.6 mg/dl despite fluid bolus should have their cisplatin dose for that day held. Patients with serum creatinine >2.0 µg/dl are at serious risk for acute renal failure and, thus, should have their cisplatin held for the remainder of that particular cycle.

Hyponatremia is usually mild and does not require therapy; however, hypomagnesemia requires aggressive replacement therapy. If a patient develops hypomagnesemia in the hospital despite MgSO4 i.v. replacement, this patient should always be discharged with an oral supplementation of magnesium, i.e., magnesium oxide 400 mg p.o. three times per day and have the magnesium levels checked initially twice per week. If the magnesium drops to <1 mEq/l, it should be replaced i.v., i.e., 32 mEq in 500 ml NS i.v. over 2 h. The oral magnesium supplementation should be maintained throughout the biochemotherapy program and for at least 3 weeks after completion of the last cycle, because the magnesium continues for many weeks after the biochemotherapy is discontinued. Because oral magnesium formulation may produce diarrhea, it should be avoided during periods of diarrhea, and i.v. replacement should be used during this period.

**Infection**

**Description.** The incidence of infection with the biochemotherapy protocols is clearly higher than for chemotherapy-alone programs. The major factors that lead to the increased infection rate are the more prolonged neutropenia, IL-2-mediated impairment of neutrophil function (30), IL-2 skin toxicity, and frequent accessing of the central line. In fact, in the initial Phase II concurrent biochemotherapy regimen at M. D. Anderson, 64% of the patients developed febrile neutropenia and 45% frank bacteremia (9). In these initial trials, all patients had an indwelling catheter that remained throughout the whole biochemotherapy treatment and was the most common site of infection. The most common bacterial organisms included coagulase-negative staphylococci (77%), Staphylococcus aureus (7%), and Gram-negative bacteria (15%).

In the modified concurrent biochemotherapy regimen, routine antibiotic and G-CSF prophylaxis was instituted in an effort to reduce the incidence of bacteremia (12). In addition, it was required that central venous catheters be removed at the end of each 5-day inpatient treatment cycle. These modifications reduced the incidence of significant infections to <5%. Only two episodes of catheter-related infection were observed in 44 patients treated with this approach (12).

At the Hospital Sírio-Libanês, the use of an antibiotic-coated catheter called Spectrum (Cook, Inc., Bloomington, IN) only during the hospital stay has been associated with a dramatic reduction in the incidence of infection; there was only 1 catheter-related infection among 30 patients treated. In contrast,
**Table 4** Example of a concurrent biochemotherapy order

<table>
<thead>
<tr>
<th>Order Description</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-cisplatin hydration with NS 1000 mg i.v. over 2 h (add Mannitol 20%)</td>
<td>1</td>
</tr>
<tr>
<td>Cisplatin 20 mg/m² in 1000 ml NS i.v. over 2 h on days 1–4</td>
<td>1</td>
</tr>
<tr>
<td>DTIC 800 mg/m²/i.v. over 1 h on day only</td>
<td>1</td>
</tr>
<tr>
<td>Vinblastine 1.6 mg/m² IVP on days 1–4</td>
<td>1–4</td>
</tr>
<tr>
<td>IL-2 9 MIU/m²/day in 250 ml D5W with 1 ml of 25% albumin i.v. by continuous infusion over 4 days (36 MIU/m² i.v. continuous infusion over 96 h)</td>
<td>1–4</td>
</tr>
<tr>
<td>IFN-α 5 MU/m² s.c. on days 1–5</td>
<td>1–5</td>
</tr>
<tr>
<td>G-CSF 300 or 480 µg s.c. on days 6–14 (or until absolute neutrophil count ≥ 5,000/µl)</td>
<td>1–6</td>
</tr>
<tr>
<td>Erythropoietin 40,000 units s.c. weekly, starting on day 6</td>
<td></td>
</tr>
</tbody>
</table>

O’Day *et al.* (10) from the John Wayne Cancer Center reported a 42% incidence of infection, of which the vast majority was catheter related in patients that were discharged with an indwelling central venous catheter despite the use of G-CSF. Thus, the removal of the central venous catheter after each 5-day treatment course appears to be the most critical component of the strategy to reduce infection in patients receiving biochemotherapy.

**Management.** We favor the insertion of a central venous catheter prior to each treatment and removal when the patient is discharged. Despite the inconvenience and discomfort for the patient, the virtual elimination of catheter-related infections and hospital admissions because of infections justifies this approach. We also recommend prophylactic administration of an oral antibiotic (usually cephalixin 500 mg p.o. twice per day) at the beginning of each cycle of biochemotherapy, continuing until about day 15 and the administration of G-CSF from days 5 or 6 until at least absolute neutrophil count ≥ 5,000/µl (usually by day 15 of each treatment cycle). In addition, patients experiencing fevers after day 3 should be assumed to potentially have an infection. We recommend routinely obtaining blood cultures in this setting, and in patients with other findings suggestive of infection (*i.e.*, hypotension, purulent drainage at the catheter site, severe skin rash manifested by moist desquamation, or neutropenia), broad spectrum i.v. antibiotics should be initiated, *i.e.*, Vancomycin plus a third or fourth generation cephalosporin or a carbapenem (*i.e.*, Cefepime or Meropenem). Vancomycin is critical because coagulase-negative staphylococci is very prevalent in IL-2-treated patients (9–11). Quantitative blood cultures, one from the central line and one from the peripheral line, should be obtained to help determine whether the infection is catheter related. Patients with documented neutropenic infection should have a 25% reduction in DTIC and vinblastine doses for subsequent cycles of therapy.

**Cutaneous and Mucosal**

**Description.** All patients experience some degree of acute skin toxicity manifested usually as diffuse erythema or maculopapular rashes. The skin rash is very mild on the first day of therapy and gets gradually worse by the end of the IL-2 therapy (day 5). It usually resolves within 5 days after completion of the IL-2 infusion (Fig. 2). In some patients, the rash is associated with severe itching. Dry skin and mild to moderate exfoliation of the skin are common in the latter 2 weeks of the 3-week biochemotherapy cycle (Fig. 2). In ~20% of the patients, we observed a painful oropharyngeal erythema, apparently not caused by infectious agents but related to the IL-2 therapy. It subsides 2–4 days after discontinuation of the IL-2 therapy but can be more noticeable in patients that receive more than two cycles of therapy. Vitiligo is mild after two cycles of therapy but can be more noticeable in patients that receive more than two cycles of therapy. It subsides 2–4 days after discontinuation of the IL-2 therapy but can be more noticeable in patients that receive two cycles of therapy. It subsides 2–4 days after discontinuation of the IL-2 therapy but can be more noticeable in patients that receive more than two cycles of therapy.

**Management.** No specific therapy should be applied for the skin rash. For pruritus, prescribe hydroxyzine 50 mg p.o. every 6 h on a PRN basis. Do not use corticosteroids of any type. To minimize dry skin and exfoliation of the epidermis, we recommend frequent use of emollients, which should be left in the patient’s room at the beginning of the therapy.

**Endocrine**

**Description.** Hypothyroidism is clearly associated with high-dose IL-2 therapy, with an incidence ranging from 21 to 47% (33–35). However, the precise incidence of this toxicity with concurrent biochemotherapy has not been established, because it has not been evaluated systematically. It is important to emphasize that hypothyroidism may be difficult to diagnose in patients with metastatic cancer because the symptoms of hypothyroidism, such as fatigue and elevation of the lactic dehydrogenase, may mimic clinical recurrence, easily misleading the clinician. In IL-2-treated patients complaining of fatigue, hypothyroidism should always be considered in the differential diagnosis.

**Management.** Monitoring of thyroid function tests every 3 months is advisable. Only replacement therapy with levothyroxine is necessary to keep thyroid-stimulating hormone levels within the normal limits.

**Table 5** Essential components of an ancillary biochemotherapy order sheet

1. D5/1/2 NS with KCl 20 mEq/l plus MgSO₄ 8 mEq/l at 125 ml/h
2. Acetaminophen 650 mg p.o. every 6 h
3. Prochlorperazine 10 mg (or droperidol 2.5 mg) i.v. plus diphenhydramine 50 mg i.v. every 6 h (ATC on days 1 and 2)
4. Prochlorperazine 10 mg (or droperidol 2.5 mg) i.v. plus diphenhydramine 50 mg i.v. every 4 h PRN nausea or vomiting
5. Meperidine 50–75 mg i.v. every 4 h PRN chills
6. Monitor blood pressure, pulse, temperature, and urine output every 4 h
7. If systolic blood pressure < 90 mm Hg, give 500 ml NS i.v. over 30 min
8. If urine output < 100 ml/h, give 500 ml NS i.v. over 30 min. If urine output does not improve, start dopamine at 2 µg/kg/min
9. If temperature is > 39.5°C, naproxen 375 mg p.o. × one dose
10. Loperamide 4 mg (2 tablets) p.o. every 4 h PRN diarrhea
11. Do not use corticosteroids of any type
12. Check creatinine, sodium, potassium, and magnesium on days 3 and 5. Check CBC on day 5.
Neurological

**Description.** Peripheral neuropathy is attributable primarily to cisplatin and to a lesser extent to vinblastine and is manifested as numbness in the toes and sole of the foot and less commonly in the tip of the fingers. This symptomatology may evolve to pain. It is common in patients who receive more than four or more cycles of therapy. In ~20% of the patients, it can be severe (grade 3 or 4), with patients complaining of pain particularly when they stand for prolonged periods of time (9). The peak symptoms do not occur until 1–3 months after completion of the biochemotherapy program; therefore, any symptoms during therapy must be taken seriously and treatment modified accordingly.

During the hospital stay, insomnia is common in great part because of the frequent monitoring of the vital signs and urine output. Neuropsychological effects, such as failure in the cognitive performances, increased latency, and depression, also occur but are often underdiagnosed. Although confusion is a common dose-limiting toxicity of high-dose IL-2-alone regimens, it is rarely seen with biochemotherapy. In fact, only 2 of 44 patients receiving the modified concurrent biochemotherapy regimen developed CNS toxicity (12). Both of these patients had undergone prior cranial radiation for CNS metastases, indicating that such prior therapy is likely a risk factor for CNS toxicity. Rarely, myositis with rhabdomyolysis has been reported (36, 37).

**Management.** There is no optimal therapy for cisplatin-related peripheral neuropathy. In our experience, gabapentin 300 mg p.o. on the first day, 300 mg p.o. twice per day on the second day, and 300 mg p.o. three times per day from the third day after is highly effective in controlling painful neuropathic symptoms. Gabapentin does not affect the numbness, however. Insomnia responds readily to lorazepam 1–2 mg at bedtime. At the earliest symptoms of depression, we start Sertraline 50 mg p.o. every day and maintain this antidepressant throughout the remainder of the biochemotherapy program.

Miscellaneous

It is important to know that patients treated with high-dose IL-2 are more likely to experience hypersensitivity reactions to cisplatin or DTIC (38). Likewise, patients treated with IL-2-based regimens are more prone to adverse reactions to i.v. contrast, particularly within 2 weeks of the IL-2 therapy (39).

Concurrent Biochemotherapy and Ancillary Orders

To help the practicing oncologist, we have provided a sample of a biochemotherapy order sheet (Table 4). We have also provided a sample of an admitting order sheet, which is routinely used for the concurrent biochemotherapy regimen (Table 5). Use of such sample sheet should help avoid inadvertent omission of important parameters and standing orders. We also favor providing a calendar upon discharge that describes treatment and scheduled tests and an information sheet describing worrisome side effects that should prompt a call to the covering physician.

References


Practical Guidelines for the Management of Biochemotherapy-related Toxicity in Melanoma

Antonio C. Buzaid and Michael Atkins

*Clin Cancer Res* 2001;7:2611-2619.