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Current Status of Interleukin-2 Therapy for Metastatic Renal Cell Carcinoma and Metastatic Melanoma

An estimated 32,000 new cases of renal cell carcinoma and 54,000 new cases of melanoma will be diagnosed in the United States in 2002.[1] Although 70% of patients with renal cell carcinoma and 85% of patients with melanoma have local or locally advanced disease at diagnosis, many of these patients will develop metastatic disease.[2,3] The median survival time for metastatic renal cell carcinoma patients after diagnosis is 8 to 12 months; the 5-year survival rate is 0% to 20%.[4,5] Prognosis for metastatic melanoma patients is even more dismal; the median survival time is 6 to 8.5 months, with 5-year life expectancy less than 10%.[6]

Traditionally, surgery has been the most effective therapy for renal cell carcinoma, but the poor survival rates (5-yr survival rate, 2%) in patients with distant metastases, have limited this approach.[4] Radiation therapy has also yielded disappointing results and is only used palliatively in these patients.[2,5] Furthermore, renal cell carcinoma is resistant to chemotherapy. In a review of approximately 4,000 renal cell carcinoma patients receiving more than 40 chemothera-

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peutic agents in phase II clinical trials, the overall response rate was 0–15%.[7A]

Similarly, effective therapies for metastatic melanoma are also limited. Surgery and radiation therapy are used only for palliation and to improve quality of life.[7B] Single-agent chemotherapy produces modest overall response rates (10% to 20%) in metastatic melanoma patients, but complete responses are rare.[8] Although combination chemotherapy

produces higher overall response rates compared with single-agent chemotherapy, this approach produces greater toxicity and does not prolong survival time.[8] Therefore, the use of chemotherapy in the treatment of metastatic melanoma remains controversial, and its use is often limited to clinical trials.[8]

The resistance of both metastatic renal cell carcinoma and melanoma to traditional oncology-related treatments has generated widespread in-

ABSTRACT

Interleukin-2 (IL-2, Proleukin) is one of the most effective agents in the treatment of metastatic renal cell carcinoma and metastatic melanoma. High-dose IL-2 therapy produces overall response rates of 15% to 20%; however, it is associated with significant toxicities that affect essentially every organ system. Although IL-2-related toxicities are usually reversible with therapy discontinuation, alternative IL-2 regimens have been evaluated. Several phase II studies have demonstrated that administering lower doses of IL-2 by IV bolus or continuous IV infusion or subcutaneously produces overall response rates similar to those with high-dose IL-2 therapy; however, randomized clinical trials have not yet been completed. In renal cell carcinoma, combining IL-2 with interferon alfa (Intron A, Roferon-A) or chemotherapy agents produces similar or increased overall response rates compared with the response rates of IL-2 alone, with no survival advantage. Combination IL-2 regimens in metastatic melanoma patients have produced variable results. The most promising regimens have included various IL-2-based biochemotherapy regimens in other patients. Randomized studies confirming the superiority of these regimens over high-dose IL-2 therapy are needed.

terest in developing and evaluating other effective therapies, such as immunotherapy. The relationship between the immune system and renal cell carcinoma and melanoma is suggested clinically; for example, spontaneous regression of renal cell carcinoma and melanoma in some patients suggests that these malignancies may be responsive to the patient's immune system.[3,9] Thus, enhancing a patient's immune system with cytokines is a rational treatment approach. Both interferon alfa (IFN- α , Intron A, Roferon-A) and interleukin-2 (IL-2, Proleukin) are effective therapies for these malignancies. Interferon alfa and IL-2 have produced overall response rates of 10% to 15% and 15% to 20%, respectively, in metastatic renal cell carcinoma and melanoma patients.

While IFN- α has been approved and is considered standard in the adjuvant treatment of melanoma, only IL-2 is approved by the US Food and Drug Administration for the treatment of metastatic renal cell carcinoma and melanoma.[2,7,10]

Pharmacology of IL-2

IL-2, first identified as a T-cell growth factor in 1976, is a 15-kd glycoprotein produced primarily by T-helper cells.[2,11,12] Interaction of IL-2 with the IL-2 receptor, which is expressed in increased amounts on activated T cells, results in proliferation and differentiation of both B and T cells, cytotoxic cells, and stimulation of a cascade of cytokines, including various interleukins, interferons, and tumor necrosis factors.[12] The antitumor effect of IL-2 is mediated by its ability to cause proliferation of natural killer cells (NK), lymphokine-activated killer cells (LAK), and other cytotoxic cells.[12]

IL-2 Doses and Administration Methods

Various administration schedules and doses of IL-2 have been evaluated. High dosage IL-2 (600,000–720,000 IU/kg IV q8h) is the most commonly used regimen in the United States.[2] The FDA-approved dos-

age for treatment of metastatic renal cell carcinoma or melanoma is 600,000 IU/kg administered by IV bolus over 15 minutes every 8 hours for a maximum of 14 doses.[13] Following 9 days of rest, the regimen is repeated, if tolerated by the patient.[13] In Europe, the approved method of IL-2 administration is by continuous intravenous infusion (18 million IU/m²/d for two 4.5–5-day cycles, with 6–8 days of rest between cycles).[12] Dosages up to 24 million IU/m²/d IV administered over 24 hours have also been evaluated.[2] Low-dose subcutaneous IL-2 regimens (1–30 million IU/m²/d) have been investigated because they may reduce toxicity without compromising efficacy.[2]

Adverse Events

The toxicity profile of IL-2 is dose, route, and administration dependent.[2] This supplement includes an article titled *Managing Toxicities of High-Dose IL-2*, which more fully discusses the type, incidence, and management of toxicities associated with high-dose IL-2 therapy.

Use of IL-2 in Renal Cell Carcinoma

High-Dose IL-2

The 1992 FDA approval of high-dose IL-2 therapy for patients with metastatic renal cell carcinoma was based on the pooled results of seven phase II studies conducted at 21 institutions.[5,14] In these studies, IL-2 600,000 IU/kg (five studies) or 720,000 IU/kg (two studies) was administered as an IV bolus every 8 hours for 14 consecutive doses over 5 days, as tolerated.[5] After 5 to 9 days of rest, an additional cycle was administered as tolerated. Courses (ie, two cycles) were repeated if patients displayed tumor response or disease stabilization.

Patients were continually monitored for response rates, remission durations, and survival times. The most recent overall response rate reported was 15%, and the complete response rate was 7%.[14] Responses were durable, with a median duration of response of 54 months (range,

3–131+ months).[14] Complete responders tended to have a longer duration of response than patients who achieved only a partial response (80+ vs 20 months, respectively), but the median duration of response for complete responders has not yet been reached.[14] Baseline performance status (PS) was the only predictor of response: patients in relatively good health at therapy initiation, Eastern Cooperative Oncology Group (ECOG) performance status of 0, had almost twice the rate of overall response as that of patients with a poor baseline performance status, 17% for ECOG PS, 0 and 9% for ECOG PS, 1; $P = .03$.[5] The median survival time was 16.3 months, which is higher than the historical median survival time for patients with metastatic renal cell carcinoma who do not receive high-dose IL-2.[4,14] This difference, however, may be attributed to the higher performance status and other favorable characteristics of patients who meet the rigorous eligibility requirements for high-dose IL-2 therapy. Additionally, 10% to 20% of patients are estimated to achieve a long-term (5–10 year) survival benefit.[14] Baseline performance status ($P < .01$), prior nephrectomy ($P < .01$), and time from diagnosis to treatment ($P = .01$) were the most important predictors of survival.[5]

Severe (grades 3/4) toxicities developed in most patients.[5] The most common toxicity was hypotension, which occurred in 96% of patients (grades 3/4, 74%). Other severe toxicities resembled other clinical manifestations of septic shock. Most toxicities reversed rapidly after IL-2 discontinuation, and 89% of patients were discharged within 7 days of initial treatment. Despite the reversibility of toxicities, 4% of patients died of treatment-related toxicity in these early clinical trials. Since these trials were conducted, however, an under-

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Table 1

Efficacy Results of Randomized Phase III Clinical Trials Evaluating Interleukin-2–Based Biochemotherapy in Renal Cell Carcinoma

Study	Regimen	Number of Assessable Patients	Overall Response Rate	Complete Responses	Partial Responses	Median Duration of Response	Median Survival Time
Atzpodien et al[27]	5-FU, IL-2, IFN- α^a Tamoxifen ^b	41	39.1%	17.1%	21.9%	Not reported	24 mo
		37	0%	0%	0%	Not applicable	13 mo ^c
Naglieri et al[29]	IL-2, IFN- α^d Epirubicin, IL-2 ^e	18	11%	5.5%	5.5%	12 mo	18 mo+
		20	10%	5%	5%	6 mo	26 mo
Négrier et al[28]	IL-2, IFN- α^f 5-FU, IL-2, IFN- α^h	70	1.4%	0%	1.4%	Not reported	Not reported ^g
		61	8.2%	0%	8.2%	Not reported	Not reported ⁱ

^a5-FU 1,000 mg/m²/d d1 of wk 5–8; IL-2 10 million IU/m² subcutaneously twice daily d3–5 of wk 1 and 4 and 5 million IU/m²/d subcutaneously d1,3,5 of wk 2 and 3; IFN- α 5 million IU/m²/d subcutaneously d1 of wk 1 and 4, 5 million IU/m²/d subcutaneously d1,3,5 of wk 2 and 3, 10 million IU/m²/d subcutaneously d1,3,5 of wk 5–8. 8-wk treatment cycles repeated up to three courses.

^bTamoxifen 80 mg po twice daily. 8-wk treatment cycles repeated up to three courses.

^c*P* = .0325, 1st vs 2nd regimen.

^dIL-2 9 million IU/d subcutaneously d1,2, followed by 4.5 million IU/d subcutaneously d3–5 of wk 1 and d1–5 of wk 2–6; IFN- α 3 million IU/d subcutaneously d1,3,5 of wk 1–6. Treatment cycles repeated every 10 wk.

^eEpirubicin 25 mg/m²/d d1,8,15,22,36; IL-2 9 million IU/d subcutaneously d1–2, followed by 4.5 million IU/d subcutaneously d3–5 of wk 1 and d1–5 of wk 2–6. Treatment cycles repeated every 10 wk.

^fIL-2 9 million IU/d subcutaneously d1–6 of wk 1,3,5,7; IFN- α 6 million IU/d three times weekly, wk 1,3,5,7. Two 8-wk cycles administered.

^g1-yr survival rate = 53%.

^h5-FU 600 mg/m²/d continuous IV infusion d1–5 of wk 1,5; IL-2 9 million IU/d subcutaneously d1–6 of wk 1,3,5,7; IFN- α 6 million IU/d three times weekly, wk 1,3,5,7. Two 8-wk cycles administered.

ⁱ1-yr survival rate = 52%.

5-FU = fluorouracil; IFN- α = interferon- α ; IL-2 = interleukin-2; IV = intravenous.

standing of the mechanism of the toxicity, improved patient selection, and better management techniques has evolved, contributing to the overall safety of high-dose IL-2 administration.[5]

Continuous Intravenous IL-2

Because high-dose IL-2 therapy causes significant toxicity, various doses and routes of administration have been evaluated to achieve reduced toxicity without compromised efficacy. The short half-life and rapid clearance of IL-2 administered by IV bolus prompted investigators to administer IL-2 as a continuous IV infusion. Most studies administered IL-2 at 9 to 18 million IU/m²/d for 4 to 5 days, but doses up to 24 million IU/m²/d have also been evaluated.[2] Overall response rates have varied, but the results of recent, multiple, phase I and II studies of 922 patients receiving IL-2 by continuous IV infusion showed an overall response rate of 13.3%.[10,15] Long-term survival following continuous IV infu-

sion IL-2 therapy has also been reported recently. Negrier and colleagues[16] conducted three phase II trials, in which 281 European patients receiving IL-2 18 million IU/m²/d by continuous IV infusion experienced a median survival time of 10 months. The overall 5-year survival rate was 6%, although 60% of patients with a complete response were alive at 5 years.

The results of a randomized, phase III study evaluating continuous IV infusion IL-2, subcutaneous IFN- α , and a combination of the two agents, showed an overall response rate of 6.5% in 138 patients receiving continuous IV infusion IL-2 (18 million IU/m²/d day 1–5 and 12–16) (see “Combination IL-2 Regimens: IL-2 and IFN- α ” for more study details on page 8).[17] Although the dose of IL-2 administered in this study was lower than those administered in high-dose IV bolus regimens, significant toxicity occurred. The most common severe (grades 3/4) adverse events were hypotension requiring maximal

vasopressor support (68% of patients) and fever (43%). Grades 3/4 pulmonary, renal, and cardiac adverse events occurred in approximately 15% of patients. No treatment-related deaths were reported, and all patients recovered from toxicity after IL-2 discontinuation.

Similarly, the results of the only randomized study comparing the coadministration of LAK cells with either high-dose IL-2 (594,000 IU/kg q8h days 1–5 and 11–15) or continuous IV infusion IL-2 (18 million IU/m²/d days 1–5 and 22.5 million IU/m²/d days 11–16) in renal cell carcinoma patients showed a high incidence of life-threatening toxicities with continuous IV infusion IL-2 therapy coadministered with LAK cells.[18] Fever, infection, and elevated alkaline phosphatase levels were more common in the continuous IV infusion group, and thrombocytopenia was more common in the high-dose IL-2 group. Overall response rates were similar: 20% in patients receiving high-dose IL-2 and 15% in the continuous IV infusion group.

Table 2

Efficacy Results of Randomized Phase III Clinical Trials Comparing Interleukin-2 Biochemotherapy With Chemotherapy or Immunotherapy in Metastatic Melanoma

Study	Regimen	Number of Assessable Patients	Overall Response Rate	Complete Responses	Partial Responses	Median Duration of Response	Median Survival Time
Atzpodiën et al[36]	Cisplatin, carmustine, dacarbazine, tamoxifen ^a	60	29.9%	13.3%	16.6%	15 mo	13 mo
	Cisplatin, carmustine, dacarbazine, tamoxifen, IL-2, IFN- α ^b	64	34.3%	10.9%	23.4%	9 mo	12 mo
Eton et al[37]	Cisplatin, vinblastine, dacarbazine ^c	91	25% ^d	2%	23%	Not reported	9.2 mo
	Cisplatin, vinblastine, dacarbazine, IL-2, IFN- α ^e	92	48%	7%	41%	Not reported	11.9 mo
Keilholz et al[35]	IFN- α , IL-2 ^f	66	18% ^g	6%	12%	17 mo	9 mo
	IFN- α , IL-2, cisplatin ^h	60	33%	5%	28%	6 mo	9 mo
Ridolfi et al[6]	Cisplatin, dacarbazine, carmustine ⁱ	89	20.2%	3.4%	16.8%	6.9 mo	9.5 mo
	Cisplatin, dacarbazine, carmustine, IL-2, IFN- α ^j	87	25.3%	3.4%	21.8%	8.3 mo	11 mo
Rosenberg et al[38]	Tamoxifen, cisplatin, dacarbazine ^k	52	27%	8%	19%	11 mo	15.8 mo
	Tamoxifen, cisplatin, dacarbazine, IFN- α , IL-2 ^l	50	44%	6%	38%	6 mo	10.7 mo

^a Cisplatin 35 mg/m²/d IV d1–3; carmustine 150 mg/m²/d IV d1 (cycles 1 and 3 only); dacarbazine 220 mg/m²/d IV d1–3; tamoxifen 20 mg/m²/d po qd.

^b Cisplatin 35 mg/m²/d IV d1–3; carmustine 150 mg/m²/d IV d1 (cycles 1 and 3 only); dacarbazine 220 mg/m²/d IV d1–3; tamoxifen 20 mg/m²/d po qd; IL-2 10 million IU/m²/d subcutaneously d3–5 of wk 4 and 5 million IU/m²/d subcutaneously d1, 3, 5 of wk 5; IFN- α 5 million IU/m²/d subcutaneously d1 of wk 4 and d1, 3, 5 of wk 5.

^c Cisplatin 20 mg/m²/d IV d1–4, 22–25; vinblastine 2 mg/m²/d IV d1–4, 22–25; dacarbazine 800 mg/m²/d IV d1,22.

^d $P = .001$, 1st and 2nd regimen.

^e Cisplatin 20 mg/m²/d IV d1–4, 22–25; vinblastine 1.5 mg/m²/d IV d1–4, 22–25; dacarbazine 800 mg/m²/d IV d1,22; IL-2 9 million IU/m²/d continuous IV infusion d5–8, 17–20, 26–29; IFN- α 5 million IU/m²/d subcutaneously d5–9, 17–21, 26–30.

^f IFN- α 10 million IU/m²/d subcutaneously d1–5; IL-2 18 million IU/m²/dose continuous IV infusion q 6 on d3, 18 million IU/m²/dose continuous IV infusion q12h on d4, 18 million IU/m²/dose continuous IV infusion q24h on d5, 4.5 million IU/m²/dose continuous IV infusion q24h on d6–8. Administered every 4 wk for a maximum of four cycles.

^g $P = .04$, 1st vs 2nd regimen.

^h IFN- α 10 million IU/m²/d subcutaneously d1–5; IL-2 18 million IU/m²/dose continuous IV infusion q6h on d3, 18 million IU/m²/dose continuous IV infusion q12h on d4, 18 million IU/m²/dose continuous IV infusion q24h on d5, 4.5 million IU/m²/dose continuous IV infusion q24 on d6–8; cisplatin 100 mg/m²/d d1. Administered every 4 wk for a maximum of four cycles.

ⁱ Cisplatin 75 mg/m²/d IV d1; dacarbazine 800 mg/m²/d IV d1; optional carmustine 150 mg/m²/d IV d1, every 21d for a maximum of six cycles.

^j Cisplatin 75 mg/m²/d IV d1; dacarbazine 800 mg/m²/d IV d1; optional carmustine 150 mg/m²/d IV d1; IL-2 4.5 million IU subcutaneously d3–5, 8–12; IFN- α 3 million IU IM d3,5 of wk 1, then three times q wk, wk 2, 3. Each cycle administered every 21d for a maximum of six cycles. After sixth cycle, patients continued to receive IL-2 4.5 million IU subcutaneously 8d/mo and IFN- α 3 million IU IM three times q wk up to mo 12.

^k Tamoxifen 40 mg po d1, followed by 10 mg po bid d2–29; cisplatin 25 mg/m²/d IV d2–4, 23–25; dacarbazine 220 mg/m²/d IV d2–4, 23–25.

^l Tamoxifen 40 mg po d1, followed by 10 mg po bid d2–29; cisplatin 25 mg/m²/d IV d2–4, 23–25; dacarbazine 220 mg/m²/d IV d2–4, 23–25; IFN- α 6 million IU/m²/d subcutaneously d5–8, 26–29; IL-2 720,000 IU/kg IV q8h until patient becomes tolerant.

IFN- α = interferon- α ; IL-2 = interleukin-2; IM = intramuscular; IV = intravenous.

Subcutaneous IL-2

Interleukin-2 (1–30 million IU/m²/d) administered subcutaneously has also been evaluated in renal cell carcinoma patients, particularly in those who may not be eligible for high-dose IL-2 therapy, such as patients with poor performance status or major organ

dysfunction.[2,13] Multiple phase II clinical trials have been performed, but many of these trials enrolled fewer than 25 patients.[2] Results of a recent review of almost 300 patients receiving subcutaneous IL-2 therapy in multiple phase II trials showed an overall response rate of 16.8% and a

complete response rate of 3%.[10,15]

The common use of one of the subcutaneous IL-2 regimens is based on the results of a large study conducted by Sleijfer, Buter, and colleagues.[19,20] In this study, unlike high-dose IL-2 studies, patients were not excluded because of poor perfor-

mance status, concomitant conditions, or age.[5,19] An unselected, consecutively enrolled group of 47 metastatic renal cell carcinoma patients received subcutaneous IL-2 (week 1: 18 million IU qd days 1–5; weeks 2–6: 9 million IU qd days 1–2 and 18 million IU qd days 3–5) for 4 to 6 consecutive weeks on an outpatient basis.[20] An overall response rate of 20% was observed. Two patients experienced complete responses and had durable remission times (29 and > 35 months). The median survival time of all patients was 12 months. Almost 50% of the patients who responded were at least 65 years old, indicating that subcutaneous IL-2 is an effective and safely administered regimen in patients often excluded from receiving high-dose IL-2.

An ongoing randomized, phase III NCI study in patients eligible to receive high-dose IL-2 therapy is evaluating a high-dose IV bolus (720,000 IU/kg q8h for a maximum of 15 doses/course; 30 doses/course), an intermediate-dose IV bolus (72,000 IU/kg q8h for a maximum of 15 doses/course; 30 doses/course), and an outpatient subcutaneous IL-2 regimen (week 1: 250,000 IU/kg/d days 1–5; weeks 2–6: 125,000 IU/kg/d days 1–5).[21] Interim study results, after a median follow-up of 27 months, showed overall response rates of 16%, 4%, and 11% in the high-dose, intermediate-dose, and subcutaneous IL-2 regimens, respectively. As expected, toxicity was greatest in the high-dose IL-2 group, but quality of life did not differ among the three regimens.[22,23] Since response duration has not been evaluated, definitive conclusions regarding the efficacy and toxicity of these regimens are premature. While awaiting final study results, clinicians should individualize the IL-2 schedule, dose, and route of administration according to the patient's clinical status, comorbidities, familiarity of the physician with IL-2 therapy, and desirability of inpatient or outpatient therapy.[21]

Combination IL-2 Regimens

• **IL-2 and IFN- α** —Because both IL-2 and IFN- α are effective single agents in the treatment of renal cell

carcinoma, and the results of preclinical studies in animal models have suggested a synergistic antitumor effect of the combination, many phase I and II clinical trials have evaluated the combination of IL-2 and IFN- α in metastatic renal cell carcinoma patients.[10] Patients received various doses of both agents; various methods of IL-2 administration were also used, although most patients received IL-2 subcutaneously.[10] A recent review of these early study results from more than 1,600 patients showed an overall response rate of approximately 20%, regardless of the method of IL-2 administration.[15] Individual clinical trial results reported overall response rates of 0% to greater than 30%.[2] The overall response rates observed with this combination were similar to those of high-dose IL-2 therapy, but the duration of response tended to be shorter.[24] For example, in a follow-up at 5 years of patients receiving outpatient IL-2 (5 million IU/m²/dose subcutaneous q8h x 3, then daily) and IFN- α (5 million IU/m²/dose subcutaneous three times/week), the median duration of response was 12 months (range, 1–49+ months), much lower than the median duration of response of 54 months reported in patients receiving high-dose IL-2.[14,24]

Results of randomized, phase III clinical trials evaluating the combination of IL-2 and IFN- α compared with single agent IL-2 or IFN- α have varied. Négrier and colleagues [17] reported a significantly higher overall response rate with continuous IV infusion IL-2 and IFN- α compared with IL-2 or IFN- α alone (18.6%, 6.5%, and 7.5%, respectively; $P < .01$ for combination vs IL-2 or IFN- α); however, no significant difference in overall survival times was reported. Patients receiving IL-2 alone or the combination experienced more grade 3/4 adverse events than did patients receiving IFN- α only.

Preliminary results of a phase III randomized trial comparing low-dose outpatient IL-2 and IFN- α with high-dose IL-2 therapy suggested the superiority of single-agent, high-dose IL-2 therapy.[25] In this study, pa-

tients receiving high-dose IL-2 had a significantly higher overall response rate (26% vs 11%; $P = .01$). Preliminary overall survival data suggest that high-dose therapy also produces a longer median survival time (15 months vs 12 months; $P = .08$). Because of significant toxicity and lack of a survival advantage with the combination of IL-2 and IFN- α , the use of IL-2 alone remains the standard of care in metastatic renal cell carcinoma.

• **Biochemotherapy**—The efficacy of IL-2 combined with chemotherapy or with chemotherapy and IFN- α in metastatic renal cell carcinoma patients has also been evaluated. Results of phase II clinical trials evaluating IL-2, IFN- α , and fluorouracil were promising, with overall response rates as high as 39% and median survival times ranging from 11.9 months to more than 42 months.[26] The results of several small phase III clinical trials, however, have shown disparate results regarding overall response rates with this combination (Table 1).[27–29]

Naglieri and colleagues[29] compared the combination of IL-2 and epirubicin with that of IL-2 and IFN- α in a phase III clinical trial (Table 1). Overall response rates were similar, but the survival time was longer (although not significantly) in the biochemotherapy group (median survival time, 26 and 18+ months, respectively). Toxicity associated with biochemotherapy regimens varies, but can be moderate to severe.[10] Thus, until the superior efficacy of biochemotherapy in metastatic renal cell carcinoma patients has been demonstrated, these regimens should remain investigational.

Use of IL-2 in Melanoma

High-Dose IL-2

As with metastatic renal cell carcinoma, high-dose IL-2 is one of the most effective treatments of metastatic melanoma. Between 1985 and 1993, 270 metastatic melanoma patients enrolled in eight clinical trials received high-dose IL-2 therapy, and the results of these studies were the basis for the 1998 FDA approval of

high-dose IL-2.[21,30] In seven of the eight clinical trials, 265 patients received 600,000 to 720,000 IU/kg every 8 hours up to a maximum of 14 doses over 5 days, as tolerated.[30] Doses of 360,000 or 540,000 IU/kg were administered to five patients in the eighth study. The overall response rate was 16%, and the complete response rate was 6%. Responses were observed at all disease sites, including visceral, soft tissue, bone, cutaneous, and subcutaneous sites, and in patients with large tumor burdens. The median durable response rate was 8.9 months (1.5–122+ months), and disease has not progressed in patients responding more than 30 months.[31] Patients with a good baseline ECOG performance score (0) or who had not received prior systemic therapy were most likely to respond to high-dose IL-2 therapy.[30] The median survival time was 12 months, and 19 of the 43 responding patients (44%) have survived at least 5 years.[31]

The toxicity produced by high-dose IL-2 in these clinical trials is similar to that observed in the renal cell carcinoma studies. Hypotension was the most common toxicity, occurring in 64% of patients; grades 3/4 hypotension occurred in 45% of patients.[30] Gastrointestinal adverse events, including nausea, vomiting, and diarrhea, were also common, but were rarely life-threatening. Life-threatening (grade 4) respiratory events and ventricular tachycardia occurred in 4% and 1% of patients, respectively. Treatment-related deaths occurred in 2.2% of all patients, but no deaths occurred in the 88 patients treated after 1990, corresponding with the time interval when antibiotic prophylaxis was routinely administered.

Continuous IV Infusion and Subcutaneous IL-2

A variety of intermediate and low doses of IL-2, administered as an IV bolus, continuous IV infusion, or subcutaneously, have been evaluated in the treatment of metastatic melanoma.[32] The results of these studies are inconsistent, with overall response rates ranging from 0% to 22%; in studies producing responses, the du-

rability of response varied.[32]

The results of the studies suggest that a dose-response relationship for IL-2 is key to the successful treatment of metastatic melanoma, and to date, only the use of high-dose IL-2 produces durable responses. Investigators continue to evaluate methods of administering lower doses of IL-2 that will reduce the toxicity associated with high-dose therapy.

Combination IL-2 Regimens

• **IL-2 and IFN- α** —As with renal cell carcinoma, the combination of IL-2 and IFN- α as treatment of metastatic melanoma has been evaluated because preclinical data have suggested synergistic immunologic effects with this combination. Phase II trial results reported variable overall response rates (0%–41%) and limited data regarding duration of response and survival time.[33] Only one randomized, phase III clinical trial has compared high-dose IL-2 and IFN- α with high-dose IL-2 only; an interim analysis of the results showed no significant improvement in response with the combination.[34] Therefore, the trial was terminated prematurely, and investigators focused on initiating studies with alternative IL-2 therapies.

• **Biochemotherapy**—Based on the success of cytokines in the treatment of metastatic melanoma, biochemotherapy regimens were developed to improve efficacy, including durable remissions.[8] Initially, biochemotherapy regimens were administered sequentially because simultaneous administration raised the likelihood of enhanced toxicity; however, the sequential regimens were highly toxic because they prolonged combined and nonoverlapping toxicities.[8] Concurrent biochemotherapy regimens produce less toxicity than sequentially administered regimens, but overall toxicity is still higher than that of chemotherapy or immunotherapy alone.[8,35]

Randomized, phase III clinical trials comparing biochemotherapy with chemotherapy or immunotherapy in metastatic melanoma have produced mixed results, with overall response

rates ranging from 25.3% to 48% for biochemotherapy regimens (Table 2). [6,35–38] Some of the trials report significantly higher overall response rates and prolonged duration of responses with biochemotherapy compared with chemotherapy or immunotherapy, whereas other results revealed no difference among the regimens. None of these studies, however, were large enough to adequately detect differences in survival times.

Thus, clinicians have been awaiting the results of a large intergroup study (ECOG/Intergroup E3695) comparing concurrent biochemotherapy (cisplatin, vinblastine, dacarbazine, [CVD], IL-2, and IFN- α) with CVD alone to establish the superiority of biochemotherapy over chemotherapy.[8,32] The preliminary results of this study show no difference in response and response duration between biochemotherapy and chemotherapy (M. B. Atkins, oral communication, June 2002). Until final results, such as survival data, are available to confirm the preliminary findings, the use of biochemotherapy should be limited to a clinical trial, and high-dose IL-2 therapy should remain one of the most logical choices in patients with metastatic melanoma who can tolerate this medication.

Conclusions

IL-2-based therapy is one of the most effective treatments for either metastatic renal cell carcinoma or melanoma; however, few patients respond to treatment. Currently, high-dose IL-2 therapy appears to be more effective than IL-2 administered by alternative routes or schedules or the combination of IL-2 and IFN- α in the treatment of metastatic renal cell carcinoma and melanoma. Randomized studies comparing high-dose IL-2 with lower-dose regimens are

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currently ongoing in patients with renal cell carcinoma

Results of biochemotherapy studies in the treatment of metastatic melanoma are promising. Biochemotherapy remains unproven in the treatment of metastatic renal cell carcinoma because of the extremely limited activity of any chemotherapeutic agent and lack of randomized, comparative study results. Likewise, the use of biochemotherapy in metastatic melanoma is not the standard of care, at least until the final results of a large intergroup study comparing biochemotherapy with chemotherapy alone are reported. The optimal role of IL-2 therapy in metastatic renal cell carcinoma and melanoma is likely to evolve as newer, more effective therapies, which may enhance the cytotoxic effect of IL-2, are developed and incorporated into IL-2-based regimens. Future research should also focus on combining IL-2 with newer biologic and targeted therapies.

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