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Cognitive and Affective Symptoms Experienced by Cancer Patients Receiving High-Dose Intravenous Interleukin-2 Therapy: An Integrative Literature Review

Tara K. Mann, BSN, RN, Robin B. Dail, PhD, RN, FAAN, and Donald E. Bailey Jr, PhD, RN, FAAN

School of Nursing, Duke University, Durham, North Carolina

Abstract

Background—Alterations in cognitive/affective functioning are among the most challenging side effects experienced by 80% of patients with metastatic melanoma and metastatic renal cell carcinoma undergoing high-dose Interleukin-2 (IL-2) therapy.

Objective—The purpose of this literature review is to describe what is known about IL-2—induced cognitive/affective symptoms, their prevalence and level of severity, and synthesize findings to determine areas for future research to address symptom management challenges. This review describes the IL-2 patient experience, and the pathophysiology leading to these changes.

Methods—An online electronic search using PubMed was performed to identify relevant literature published between 1992 and 2015. Of the original 113 manuscripts, information was extracted from nine articles regarding cognitive symptoms, affective symptoms, sample size, research design, reliability and validity.

Results—Our review suggests that the trajectories, breadth and depth of cognitive/affective symptoms have yet to be described. Despite intervention studies designed to address the psychosocial complications of IL-2, an understanding of the level of altered cognitive/affective symptoms experienced by IL-2 patients remains unclear.

Conclusion—Our literature review reveals a lack of standardization when assessing, reporting and managing cognitive/affective symptoms. Patients/family members have reported cognitive/affective symptoms to be the most alarming and difficult symptoms, yet these symptoms are not adequately screened for and patients were not informed about potential changes.

Implications for Practice—Assessing patients for cognitive/affective alterations is important to reduce anxiety while improving outcomes. Education about the illness trajectory (what to expect during/after treatment) can help care partners/patients set realistic shared expectations, and increase coping.

Background

Alterations in cognitive and affective functioning are among the most challenging side effects experienced by 80% of patients with metastatic melanoma (MM) and metastatic renal cell carcinoma (RCC) undergoing high-dose Interleukin-2 (IL-2) therapy.¹ Altered cognition² includes changes in concentration, attention, short-term memory, confusion, mental fatigue, executive functioning, abstraction, language, basic arithmetic and orientation,^{3, 4} whereas affective symptoms² include mood alterations, depression, anxiety, psychosis, hallucinations, aggression, suicide ideation and coma.^{5–7} Severe cognitive/affective symptoms may result in early termination of IL-2 therapy, preventing the patient from receiving a therapeutic dose, decreasing the quality of life for patients and their informal caregivers. Furthermore, these cognitive and affective symptoms are seemingly difficult for providers to manage. In some patients, cognitive and affective symptoms continue throughout the remainder of their life.⁷ Because nurses are routinely assessing patients, and therefore can quickly identify acute changes, educating nurses in addition to family members could be beneficial in assessing for and reporting alterations in cognition and affect. Early detection of cognitive/affective symptoms will allow for all care providers to intervene earlier, potentially reducing stress and anxiety in patients and their family members, while also allowing patients to receive more therapy.

Although cognitive and affective symptoms experienced by IL-2 patients have not been extensively studied, research that has been conducted show these symptoms have a profound negative impact on patients, families, and providers.⁸ Furthermore, many of the symptoms patients and their family members describe, have not been measured and disseminated in published literature. One patient described his experience with depression and anxiety:

*On Monday, I became extremely depressed and felt a lot of panic. Panic in breathing, and in the efficacy of the treatment. I spent the day unable to think about anything but that, and it was a pretty dark day. Tuesday was more of the same with a few more brain cells firing on different things but still worry and panic.”...”
Though I had read about the side effects of IL-2, I saw more the physical side effects and didn't really consider the mental ones. I am here to tell you that they are AS DEBILITATING as the physical ones and not to be underestimated.⁹*

In 2015, the National Cancer Institute estimated 73,870 new diagnoses and 9,940 deaths secondary to melanoma,¹⁰ and 61,560 new cases and 14,080 deaths secondary to kidney cancer.¹¹ The U.S. Food and Drug Administration approved the use of IL-2 in cancer patients in 1992.¹² Patients with MM and metastatic RCC are treated with high-dose IL-2 therapy when surgery, chemotherapy and radiation therapy have been ineffective for those with stage III and IV disease. IL-2, a cytokine based immunotherapy, is given to patients with metastatic disease to stimulate their immune systems to fight off cancerous cells,¹³ and is one of the few treatments available for these patients.¹² IL-2 is a therapy shown to be beneficial specifically for clear cell RCC patients with metastatic disease, where 94% of clear cell RCC patients have carbonic anhydrase IX, a RCC marker associated with better IL-2 outcomes.¹⁴ When IL-2 is administered in high-dose, intravenous form, patients experience severe side effects.^{1, 13, 15–22} Thus far, the long-term impact of IL-2 treatments on cognition and affect has not been thoroughly described. Depression has been measured a

month after the cessation of IL-2 therapy;²³ yet, longitudinal studies of symptoms following treatment are absent in published literature. Several studies have identified cognitive (fatigue,^{15, 24, 25} confusion or disorientation,^{15, 17} seizures,^{1, 22} mental status changes¹), and affective (depression,^{23, 26} hallucinations,²² coma^{1, 15, 17}) symptoms. These studies grade the severity of these symptoms; however, absent from the literature are descriptions of when and how these symptoms present, and how they change over time. Despite severe symptoms and side effects, 33% of MM patients have some response to IL-2 treatment and 15% of MM patients show a complete response with no detectable metastases after treatment.^{16, 27} In RCC, 14% of patients show some response and 8% have a complete response.^{27, 28} Therefore, it is important to understand the depth and breadth of cognitive/affective symptoms to help patients, families and providers manage these symptoms so the patient might complete the full course of therapy.

High-dose IL-2 is defined as 600,000–720,000 International Units/kilogram (IU/kg), which is administered intravenously over 15 minutes, every eight hours for a maximum of 14 consecutive doses; these 14 doses comprise one of up to four treatment cycles.¹⁵ Despite the benefits of IL-2, managing the side effects of this treatment continues to pose a challenge for patients, family members and providers. One patient explained:

There was extreme mental craziness...I couldn't sleep, I paced the floor over and over, my brain was fried - even with sleep medication the dreams I had were just terrifying. I wasn't vocal enough with the medical staff about the things I was experiencing either. I was disoriented - and bewildered.²⁹

These quotes from patients and families highlight the importance of uncovering and understanding the wide array of cognitive and affective symptoms that patients receiving high-dose IL-2 therapy experience.

Objective

The purpose of this literature review is to describe what is known about IL-2—induced cognitive/affective symptoms, their prevalence and level of severity, and synthesize findings to determine areas for future research to address the challenges experienced by patients, family members and providers resulting from these symptoms. Patients receiving IL-2 therapy might tolerate more treatment, attain better response rates, and achieve better quality of life if life-threatening side effects are managed or reduced. This literature review describes the patient experience when undergoing high-dose IL-2, and the pathophysiology leading to these changes.

Methods

PubMed was used to identify relevant literature describing IL-2—induced cognitive/affective symptoms. Table 1 depicts the search filters, search term combinations, and manuscripts returned for each search. Results were limited to articles published after 1992, the year the Food and Drug Administration first approved IL-2 for cancer treatment.

The 113 search results from PubMed were imported into EndNote® X6 and 38 duplicates were removed. The titles and abstracts of the 75 remaining manuscripts were reviewed, and reasons for exclusion are shown in Figure 1. The bibliographic snowball technique was used to locate five additional manuscripts for inclusion.³⁰ The 20 remaining manuscripts along with the five additional manuscripts were reviewed in full text. Studies of cancers other than melanoma and RCC were excluded because standard of care dictates that IL-2 is only effective in treating patients with these specific cancers. Nine manuscripts were retained that met inclusion criteria for the review.

The Matrix Method³¹ was used to extract the nine manuscripts into a spreadsheet with the following headings: author(s), article title/journal, side effects related to IL-2 administration, definition of concepts, measures, sample, methods, strengths/weaknesses, findings, and suggested areas of future research. A synthesis of each symptom experienced by patients receiving IL-2 is presented by characteristic, severity and prevalence.

Many of the cognitive side effects reported in this literature review were graded on toxicity. The term “toxicity” refers to the level of side effect severity, and is graded by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events scale.³² The NCI grades symptom severity on a scale of 1–5; grade 1 represents “mild” side effects, grade 2 represents “moderate” requiring intervention, grade 3 represents “severe” requiring medical treatment, grade 4 represents “life-threatening” side effects resulting in hospitalization or hospice care, and grade 5 represents “death”.³²

Results

This section begins with an overview of patient demographics, attrition and prior treatments reported in empirical articles, followed by an overview of cognitive and affective symptoms experienced by patients receiving high-dose IL-2 therapy. Results associated with cognitive symptoms are in Table 2. Table 3 provides detail on each manuscript.

Demographics, Attrition, and Treatment

The median ages of patients enrolled in the high-dose IL-2 studies ranged from 42 to 52 years, with the youngest reported age of 18 years, and oldest reported age of 74 years. Large attrition rates were seen in patients receiving high-dose IL-2; only a small fraction of the population was able to receive all four cycles of IL-2 therapy. Attrition rates reported were: 7% to 58% of patients stopped treatment after cycle 1, 29% to 52% after cycle 2, 3% to 20% after cycle 3, and only 3% to 35% of patients completed the maximum four cycles of high-dose IL-2. One study reported the reasons for attrition as: patient’s choice, major depression, brain metastases/disease progression or cardiac event.²⁶ Patients received re-evaluation scans after cycle 2 of high-dose IL-2 therapy, which might explain the high attrition rate after this cycle. Patients who had disease progression (development of brain metastases or development of additional lesions) were ineligible to receive additional cycles of IL-2. Interleukin-2 therapy is contraindicated for patients with brain metastases because increased fluid in the brain is thought to place patients at a higher risk for brain lesion hemorrhage due to the increase in intracranial pressure.³³

Six articles reported the treatments that patients received prior to high-dose IL-2 therapy.^{1, 15, 17, 22, 24, 26} Of these six studies, two studies only enrolled RCC patients,^{1, 22} two studies only enrolled melanoma patients,^{15, 24} and two studies enrolled both melanoma and RCC patients.^{17, 26} Table 4 shows the treatments that melanoma and RCC patients received prior to high-dose IL-2 therapy. Over 75% of patients diagnosed with RCC had a nephrectomy. Nearly all patients with melanoma had surgery prior to treatment. Furthermore, many patients had multiple treatments prior to IL-2 therapy, including chemotherapy, previous immunotherapy, hormone therapy, radiation and/or surgery.

Cognitive Symptoms

Alterations in cognition, which include a wide array of symptoms, such as lethargy, confusion, inability to focus and sleep insufficiency are among the most challenging IL-2 side effects for patients and family members to experience and for providers to manage.^{5, 6, 34} “Cognitive fatigue” is a phrase encompassing the cognitive symptoms of IL-2, such as the symptoms listed above in addition to confusion, decreased memory, and decreased attention span. The exact etiology of IL-2—induced cognitive alterations has yet to be determined. There are two theories related to altered cognition in patients receiving high-dose IL-2 therapy: 1) changes in brain matter (white and grey matter) in chemotherapy patients³⁴ might be similar in IL-2 patients because IL-2 crosses the blood-brain barrier, and 2) alterations in cognition are related to fluid overload in the brain or cerebral edema, creating alterations in brain functioning,⁵ possibly related to capillary leak syndrome.

Fyfe and colleagues found that approximately 80% of patients experienced alterations in mental status, with more than one-fourth of IL-2 patients experiencing moderate to severe cognitive alterations.¹ Approximately a third of IL-2 patients experienced confusion,^{15, 22, 36} or severe neurotoxicity.²² Seizures in IL-2 patients are rare, although it is not clear if seizures that have been reported are related to a previous history of seizures or the development of brain metastases.^{1, 22}

It is difficult to determine what percentage of IL-2 patients are predisposed to cognitive alterations; however, cognitive fatigue impacts nearly 80% of patients receiving IL-2.¹ Fortunately, grade 3 and 4 cognitive side effects impact slightly less than 25% of IL-2 patients.¹ The low percentage of reported grade 3 and 4 cognitive side effects might be because patients who experienced severe symptoms removed themselves from therapy prior to receiving the full course of treatment.

Affective Symptoms

Affective symptoms, such as mood alterations, depression, anxiety, aggression, hallucinations and coma are difficult for patients and family members to adapt to.^{5, 6, 34} Gitlitz and colleagues reported that nearly 35% of IL-2 patients experience “hallucinations or significant neurotoxicity” but we do not know the severity, or which affective symptoms the research team defined as neurotoxic.²² The symptom of depression has been reported; however, descriptions of other affective symptoms were only found on patient list-serves designed to allow patients and their family members to discuss their disease and treatments over the internet.³⁷ Musselman and colleagues measured depression with the Hamilton

Depression Scale,²⁶ while Capuron and colleagues used the Montgomery-Asberg Depression Rating Scale to assess for depression.²³ The 21-item Hamilton Depression Scale rates scores 0–6 as “normal”, 7–17 as “mild” depression, 18–24 as “moderate” depression, and scores equal to or greater than 25 as “severe” depression.³⁸ The 10-item Montgomery-Asberg Depression Rating Scale grades scores under 10 as “normal” and scores greater than 30 as “severe” depression.³⁹ Both scales measure various dimensions of depressive symptomatology, but these researchers did not report other affective symptoms described by patients and families, such as anxiety and hallucinations.

Musselman and colleagues conducted a randomized control trial where they sought to determine if the prophylactic use of escitalopram, a selective serotonin reuptake inhibitor, reduced the level of depression in patients receiving the intervention drug.²⁶ They measured depression over consecutive cycles of IL-2 and reported a significant increase in depression with each cycle, reaching a maximum level of depression in the cycle 3. Mean scores on the Hamilton Depression Scale increased by 10 points.²⁶ Capuron and colleagues measured depression at baseline, one-week and one-month after IL-2 therapy, and found an increase in depression scores at one-week after therapy, with a significant increase at the one-month time point.²³

The etiology of changes in affective symptoms from IL-2, such as depression, mood swings, fear and tearfulness is unknown; however, pro-inflammatory cytokines that are associated with mood regulation, such as adrenocorticotrophic hormone, cortisol levels and Interleukin-6 are theorized to be a contributing factor to depression levels.²⁶ It is hypothesized that cytokine-induced depression might be related to a disruption in the metabolism of serotonin,²³ a neurotransmitter associated with mood stability and quality sleep.⁴⁰ Tryptophan is an essential amino acid precursor necessary for the synthesis of serotonin.⁴⁰ Capuron and colleagues found that a decrease in peripheral serum tryptophan levels was significantly associated with decreased appetite, pessimistic thoughts, suicide ideation and decreased concentration.²³ Because tryptophan is not produced by the body, it must be acquired through food,⁴⁰ potentially contributing to a depression cycle related to loss of appetite and inevitably lower tryptophan levels.²³

In summary, two studies measured depression,^{23, 26} and one study reported hallucinations.²² Hallucinations were reported with signs of severe neurotoxicity; therefore, we were unable to distinguish the percentage of patients who experienced hallucinations as opposed to other affective symptoms. Reports and descriptions of other affective symptoms have been neglected in the published literature thus far. The few studies measuring affective symptoms in the high-dose IL-2 population were underpowered. Sample sizes for studies were 20,²⁶ and 16 participants,²³ respectively.

Limitation of Existing Evidence

Within the reviewed literature, there was a wide array of studies varying in sample size, research design, reliability, and validity. Table 3 depicts an analysis of study methods for each manuscript used for this review. Of the nine manuscripts, seven contained empirical data,^{1, 15, 17, 22–24, 26} while two contained general information about IL-2 for patients, families and providers,^{6, 8} giving insight into known side effects and their clinical

management. Of the seven empirical studies, five used prospective methods,^{17, 22–24, 26} and two used retrospective methods.^{1, 15} Studies were conducted in as few as one site and as many as 22 research centers (multi-center research). Sample sizes ranged from 16 to 283 participants. Five of the studies used the NCI toxicity scale for rating cognitive symptom severity,^{1, 15, 17, 22, 24} while the two studies describing affective symptoms used depression scales to report symptom severity.^{23, 26}

Although studies reporting cognitive symptoms enrolled between 124 and 283 participants, internal reliability was low because of the varying treatment centers and treatment protocols, particularly in retrospective studies. Only two studies evaluated affective symptoms, and sample sizes for these studies were small, ranging from 16 to 20 participants.^{23, 26} There was a lack of standardization when assessing and screening for cognitive and affective symptoms in the high-dose IL-2 population. There appears to be a lack of consistency in the way cognitive/affective symptoms were reported, leading us to believe that each clinical facility may screen differently for cognitive/affective symptoms. Without an understanding of cognitive/affective symptoms and how they change over time in patients receiving IL-2 therapy, providers cannot know which symptoms to screen for, and the times at which screening should occur.

The lack of standardization in screening protocols may result in many symptoms being overlooked, under-reported and poorly managed. Although patients and families report sleep insufficiency as a primary concern, and researchers hypothesize that cytokines are associated with sleep disturbance, studies measuring sleep quality in the IL-2 population were not found.

Conclusion

The only identified studies measuring pre- and post-treatment changes in IL-2 symptoms were conducted by Musselman and colleagues and Capuron and colleagues;^{23, 26} these studies measured depressive symptoms in IL-2 patients. Although researchers and clinicians reported many cognitive symptoms experienced by IL-2 patients,^{1, 15, 22, 36} studies reporting cognitive symptoms did not document pre-treatment levels of these symptoms. Standardized clinician-administered scales such as the Montreal Cognitive Assessment⁴¹ and the Mini Mental Status Examination,^{26, 42} are widely used to assess for cognitive alterations in the cancer population when neuropsychological testing is time and cost prohibitive; these scales were not used in these studies. Therefore, it is difficult to determine which IL-2 patients had baseline alterations in cognition resulting from prior treatment versus patients who experienced alterations in cognition as a result of IL-2 treatment.

Interestingly, Musselman and colleagues were the only researchers to use the Mini Mental Status Examination as a screening tool for IL-2 patient eligibility.²⁶ Other researchers used the Eastern Cooperative Oncology Group performance status scores to evaluate patient eligibility for IL-2 but did not use a tool specific to cognition to measure the level of change in these symptoms.^{1, 15, 22, 24}

Discussion

The etiology of cognitive and affective symptoms is unclear and may be difficult to explore because of the complicated clinical course of cancer patients. Capillary Leak Syndrome, which is a life-threatening side effect experienced by nearly all patients receiving intravenous IL-2, causes increased vascular permeability, leading to fluid shifting out of the circulatory system and into surrounding tissue, exacerbating other negative side effects of IL-2,⁶ including cognitive and affective symptoms.⁴³

Another plausible etiology as seen in patients receiving chemotherapy is decreased and damaged white and grey matter; however, studies have not been conducted on brain matter in patients receiving immunotherapy.⁴⁴ Alterations in brain matter may possibly lead to cognitive fatigue and cognitive/affective symptoms because IL-2 crosses the blood-brain barrier; however, some researchers lean more towards the theory that alterations in cognition and affect are related to fluid overload in the brain or cerebral edema, creating changes in brain functioning.⁵ Perhaps these alterations are more severe and acute in IL-2 patients than in chemotherapy patients.

Patients and family members have reported cognitive/affective symptoms to be the most alarming and difficult symptoms related to high dose IL-2 treatment. For example, a family member described challenges of these side effects through her parent's IL-2 experience:

The second one was brutal. [Parent] could take 8 doses but the mental side effects were more severe because her brain became very swollen. This time, she did not know where she was, who I was or what was going on. She could not fall asleep for 24 hours, hallucinating all the time that she was in a mental institution and that people were trying to take her place. Then, they gave her something for anxiety and she fell asleep, waking up only to go to the bathroom. Each time she woke up for the bathroom, she fought with me because she thought that the bathroom was not where I was leading her.⁴⁵

Many patients agree that these symptoms are not adequately screened for and patients were not informed about these potential changes.⁹

Our review of the literature confirms a lack of standardization when assessing, reporting and managing cognitive/affective symptoms. Longitudinal studies describing the trajectory of depression either ended with the completion of four cycles of IL-2 therapy,²⁶ or a month after IL-2 therapy finished.²³ We were unable to locate studies describing the trajectory of cognitive symptoms. To our knowledge, a study describing the degree of neurotoxicity in relation to the number of IL-2 cycles received by the patient has not been conducted. Although patients and family members describe sleep insufficiency as problematic, studies have not been conducted to quantify this loss of sleep in IL-2 patients.

While our understanding of patient side effects related to IL-2 administration has substantially improved, many important questions remain unanswered. Perhaps the largest uncertainty is the trajectory of IL-2—induced cognitive/affective symptoms. Patients and families describe cognitive/affective alterations as worrisome and debilitating, yet little

emphasis has been placed on describing these symptoms. Furthermore, studies cannot be found that address whether patients return to baseline functioning after cessation of IL-2 therapy.

Although our review suggests altered cognition is present in high-dose IL-2 patients, the trajectories, breadth and depth of cognitive/affective symptoms have yet to be described. This is an essential step for the advancement of cognitive/affective symptom science in the IL-2 population. Despite intervention studies designed to address the psychosocial complications of IL-2, such as depression, mood swings, fear and tearfulness,²⁶ an understanding of the level of altered cognitive/affective symptoms experienced by IL-2 patients remains unclear. Without an in-depth, descriptive study elucidating the characteristics of the cognitive/affective symptoms experienced by IL-2 patients, family members and providers cannot know which symptoms to assess for in patients undergoing high-dose IL-2 therapy. Furthermore, we cannot alleviate these symptoms without an understanding of what the cognitive/affective symptoms are, the degree to which they are experienced, and how these symptoms change over time with each consecutive cycle of IL-2 therapy. Future studies should focus on describing the trajectory of cognitive/affective symptoms in the high-dose IL-2 population. A mixed-method case study approach might be beneficial to describe the experiences of patients, informal caregivers and providers, and provide insight into these symptoms, when they appear, and how they change over time.

Implications for Practice

Nurses and family members are the first line of defense when assessing for acute changes in cognition and affect, and the importance of their roles should not be minimized. It is important to reassure patients and family members that alterations in cognition and affect are prevalent and expected, and efforts should focus on techniques such as relaxation and reorienting the patient when needed.⁶ Enlisting the help of social workers, and engaging family members in techniques to maintain patient safety during times of anxiety and confusion might also be beneficial.⁶ Cognitive/affective alterations in high-dose IL-2 is multifaceted, meaning that these alterations might be the result of any or all of these factors: fluid overload, IL-2 crossing the blood brain barrier, or the many concomitant medications used to reduce other severe side effects of IL-2 treatment.³³ In addition to keen assessment skills, nurses should also determine if there are any pro re nata (PRN) medications that might be contributing to or exacerbating these alterations, for example the use of Lorazepam to assist with sleep and anxiety.

High-dose IL-2 is shown to have a plasma distribution of 13 minutes, and a plasma half-life of 85 minutes following a 5-minute bolus infusion,⁴⁶ which might explain why most side effects are transient, peaking within 2- to 4-hours after the bolus IL-2 infusion. Educating patients and family members on potential cognitive/affective alterations is essential. Education about the illness trajectory and what to expect during and after treatment has been shown to help care partners and patients set realistic shared expectations, increase coping and decrease feelings of powerlessness in the cancer population.^{47, 48} Although, most research focuses on patient interventions, care partner interventions have been found to not only help the care partner but also the patient in decreasing negative outcomes such as

depression, anxiety, and distress.^{49, 50} Nurses should institute the help of family members in assessing for acute cognitive/affective alterations, which might prove to reduce the anxiety of family members while improving outcomes for the patient. Finally, the trajectories, breadth and depth of cognitive/affective symptoms has yet to be described, which is an essential for the advancement of cognitive/affective symptom science in the IL-2 population.

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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow chart of elimination process.

Table 1

Summary of the Database Employed, Search Filters, Search Term Combinations, and Manuscript Returned for Each Search

Database	Search Filters	Search Terms	Articles Returned
PubMed	Years: 1992–2015, Human, Adult (19+ yrs), Subject: Cancer	"Interleukin-2" AND "Depression" AND "Cancer"	31
		"IL-2" AND "Depression" AND "Cancer"	25
		"Interleukin-2" AND "Cognitive" AND "Cancer"	12
		"Interleukin-2" AND "Neurologic" AND "Cancer"	9
		"Interleukin-2" AND "Behavioral"	15
		"Interleukin-2" AND "Anxiety" AND "Cancer"	8
		"Interleukin-2" AND "Psychological" AND "Cancer"	13

Abbreviations: IL-2, Interleukin-2; Yrs, Years.

Table 2

Cognitive Symptom Severity and Prevalence

Construct	Symptom	Severity and Prevalence ^I		
		All Grades	Grade 3	Grade 4
<i>Cognitive</i>	Alterations in Mental Status	80%	23%	5%
	Confusion	30–35%	13%	NR
	Somnolence	17%	3%	1%
	Seizure	1–2%	NR	NR
	Fatigue and/or delirium	81%	8%	

Abbreviations: NR, Not Reported.

^I: Grading using the National Cancer Institute Common Terminology Criteria for Adverse Events scale.

Table 3

Study Methods: Individual Extraction of Each Manuscript

Author(s)	Title	Year	Sample Size	Strengths & Weaknesses	Limitations
Atkins MB, Lotze MT, Dutcher JP, et al	High-Dose Recombinant Interleukin-2 Therapy for Patients with Metastatic Melanoma: Analysis of 270 Patients Treated Between 1985 and 1993	1999	N = 270	Strength = large sample size; Weakness = 8 different protocols in 22 different treatment centers decreasing internal reliability, also varying IV IL-2 doses received by pts	Retrospective study, inability to control for variables
Capuron L, Ravaud A, Neveu PJ, Miller AH, Maes M, Dantzer R	Association between decreased serum tryptophan concentrations and depressive symptoms in cancer patients undergoing cytokine therapy	2002	N = 16	Weakness = small sample size, different treatment protocols, international study (France)	Subcutaneous and IV IL-2 in sample
Fyfe G, Fisher RI, Rosenberg SA, et al	Result of Treatment of 255 Patients with Metastatic Renal Cell Carcinoma Who Received High-Dose Recombinant Interleukin-2 Therapy	1995	N = 255	Strength = large sample size; Weakness = different doses, 7 phase 2 trials and 21 treatment facilities	Retrospective, inconsistency in treatment dose, and facility
Gitlitz BJ, Hoffman DMJ, Moldaver N, et al	Treatment of Metastatic Renal Cell Carcinoma with High-Dose Bolus Interleukin-2 in a Non-Intensive Care Unit: An Analysis of 124 Consecutively Treated Patients	2001	N = 124	Strength = all patients received same dose, one facility, grade 3 + 4 toxicities stated	N/A
Mavroukakis SA, Muehlbauer PM, White RL, Jr., et al	Clinical Pathways for Managing Patients Receiving Interleukin 2	2001	N/A, Clinical pathway	Strength = holistic approaches to IL-2 management	Not a research study
Muselman D, Royster EB, Wang M, Long Q, Trimble LM, Mann TK, Gracia DS, McNutt MD, Auyeung NS, Oliver L, Lawson DH, Miller AH	The impact of escitalopram on IL-2-induced neuroendocrine, immune, and behavioral changes in patients with malignant melanoma: preliminary findings	2013	N = 20	Strength = prospective, randomized control trial, one clinical site, strong internal reliability and validity; Weakness = small sample size	Sample size
Rosenberg SA, Yang JC, Topalian SL, et al	Treatment of 283 Consecutive Patients With Metastatic Melanoma or Renal Cell Carcinoma Using High-Dose Bolus Interleukin 2	1994	N = 283	Strength = prospective, large sample size, all treated with same IL-2 regimen in same location, using same measurement scales; strong internal reliability and validity	N/A
Sparber AG, Biller-Sparber K	Immunotherapy and neuropsychiatric toxicity. Nursing clinical management consideration.	1993	N/A, Clinical pathway	Strength = Clinical overview of neurotoxic symptoms	Not a research study
Tarhini AA, Kirkwood JM, Gooding WE, Cai C, Agarwala SS	Durable complete responses with high-dose bolus interleukin-2 in patients with metastatic melanoma who have experienced progression after biochemotherapy	2007	N = 26	Strength = prospective, phase II trial, carried out on one inpatient unit with same protocols; Weakness = small sample size	N/A

Abbreviations: IL-2, Interleukin-2; IV, Intravenous; N, Number; N/A, Not applicable; Pts, Patients.

Table 4

Treatments Received by Patients Prior to High-Dose IL-2 Therapy

Disease	Treatment	% of Patients ^I
Melanoma	Chemotherapy	23–100%
	Hormone Therapy	1–3%
	Immunotherapy	30–35%
	Radiation	13–35%
	Surgery	96%
Melanoma and RCC²	Brain Radiosurgery	25%
	Surgery	90%
	Chemotherapy	10%
	Immunotherapy	40%
RCC	Nephrectomy	74–94%
	Immunotherapy	4–18%
	Chemotherapy	3–7%
	Hormone	4%
	Radiation	10%

Abbreviations: IL-2, Interleukin-2; RCC, Renal Cell Carcinoma.

^I: Percentages may add up to more than 100% because many patients receive multiple therapies prior to IL-2²: This study did not differentiate between melanoma and RCC patients when reporting demographic variables