Anti-Cancer Drugs, 3, pp. 567–570

Review Paper

Neurotoxicity of interferon-α

Ofer Merimsky[CA] and Samario Chaitchik
The authors are at the Department of Oncology, The Tel-Aviv Sourasky Medical Center and Sackler Faculty of Medicine, Tel-Aviv University, 6 Weizman Street, Tel-Aviv 64239, Israel. Tel: 972-3-6973494. Fax: 972-3-5469580.

Interferon (IFN) related neurotoxicity includes somnolence and confusion, fatigue, lethargy, psychiatric symptoms, conceptual disorganization, neurological deficits, cortical blindness, coma and, rarely, death. The neurologic syndromes seem to be more common in elderly patients, following intramuscular or intravenous administration, at higher doses or frequent injections of IFN-α and in primary renal cell carcinoma. The duration of the treatment was not strongly related to neurotoxicity. Computed tomography findings were non-specific and included atrophy or periventricular lucencies. Electroencephalograph studies demonstrated a generalized increase in slow wave activity which returned to normal after cessation of treatment. Behavioral and mental changes in patients treated with IFN are warning signs, and indicate the need to withdraw treatment.

Key words: Dementia, interferon-α, neurobehavioral disturbance, neurotoxicity, renal cell carcinoma.

Introduction

The widespread use of interferon-α (IFN-α) in various malignancies, such as hairy cell leukemia, renal cell carcinoma (RCC) and metastatic malignant melanoma (MM), requires familiarity with the broad spectrum side effects related to its administration. Careful treatment monitoring will minimize the risk of permanent or irreversible side effects and impairment of the patient's quality of life.

The administration of IFN-α usually induces the well known flu-like syndrome, manifested by fever, myalgia, arthralgia and malaise. Other common toxic manifestations include weakness, anorexia, nausea, vomiting, weight loss, bone marrow depression, and disturbance in liver and renal functions. Less common are cardiovascular, respiratory and central nervous system findings.

This paper aims to review the neurotoxic manifestations related to IFN-α therapy and to characterize the patient at risk of developing such a clinical syndrome.

IFN-α as a cause of the neurologic manifestations

The appearance of mental and behavioral changes in patients treated with IFN-α was attributed to the effect of IFN-α rather than to the primary disease. In our series IFN-α was the only treatment given close to the onset of dementia. Since metastatic lesions or vascular changes in the brain were not demonstrated by computed tomography, and paraneoplastic central nervous system effects of RCC were not described, the association between dementia and IFN treatment is most probable. This association is also supported by the fact that cessation of treatment resulted in complete reversal of dementia in two patients.

Mechanism of action

The mechanism by which IFN-α affects brain function is obscure. It has already been postulated that transendothelial passage of IFN from the cerebrospinal fluid (CSF) to the circumventricular organs (hypothalamus, choroid plexus, subfornical organ, area postrema) is possible through capillaries with open junctions and abundant fenestrations.[1] IFN may interfere with the activity of metabolites of arachidonic acid in the brain tissue, leading to brain vasogenic or cellular edema.[1] IFN-α may also affect the activity of neurotransmitters, e.g.

[CA] Corresponding Author

dopamine, resulting in neuropsychiatric disorders.[1] Another explanation is that neural peptides such as β-endorphin and metenkephalin exert their effect on the circumventricular organs in the diencephalon and the brain stem.[1-3] High ventricular concentration of IFN may allow for a direct modification of neuronal activity in these periventricular regions. There may also be some effects on opiate receptors in these areas.[2]

The discrepancy between the relevance of clinical symptoms and the lack of IFN-α in the CSF can be explained by the postulation that the capillaries of the circumventricular organs are more permeable to IFN-α and that there is local degradation of IFN-α in the brain.[1] In order to improve the results of treatment by IFN-α in the brain, intraventricular administration was suggested, yielding a higher response rate but more severe toxicity.[2]

Clinical manifestations and outcome

Neurologic adverse reactions to IFN-α occur in about one-third of IFN treated patients, being severe in only 7%.[4] In our series, five of 38 (13%) patients with RCC experienced neurotoxicity, being severe in only three out of the 38 patients (approximately 7%). The symptoms included somnolence and confusion, fatigue, lethargy, psychiatric symptoms and anorexia, reducing the patient into a catabolic state. The more severe derangements included conceptual disorganization, neurological deficits and coma.[1,5-8] These effects were generally reversible.[1,4,9] There was one case of irreversible bilateral cortical blindness accompanied by neurobehavioral manifestations, resulting in coma and death.[10] Irreversibility of neurotoxicity was reported by Meyers in two of 14 patients.[11] In our series three of five patients succumbed to this complication.[12]

The dominant clinical presentations in 12 of the patients treated systemically by Meyers *et al.* were cognitive changes in three, psychiatric changes in four, and cognitive or psychiatric alterations in five. Of the patients, 71% had frontal-subcortical dysfunction manifested by deficits of memory, motor coordination and frontal lobe functions. Almost 30% of the patients showed generalized decline of cognitive function, resulting in frank dementia in some of them. Parkinsonism was observed in 29%, and prominent psychiatric and emotional symptoms were found in 79%. The severity of persistent neurobehavioral symptoms did not correlate with the severity of the acute neurotoxicity.[11]

When IFN-α was injected to the brain ventricles, on-treatment neurologic manifestations included unresponsiveness, grand mal convulsion, intellectual impairment, loss of memory for recent events, lack of spontaneous speech, bilateral hearing loss and tremor. Off-treatment results were confusion, speech impairment, intellectual deterioration and, in one case, herniation and death.[2]

The general deterioration of our patients,[12] as reflected by the change in the performance status (from 90–100 to 40–70% within 1–6 months), the decrease in serum albumin level (27–39% reduction) and the rate of weight loss (10 kg/month or more), correlated with the severity of dementia. It could be that the general deterioration reflected the overall toxicity of the IFN. Progression of the disease as an explanation for physical deterioration was less likely. The course of the disease in these patients was not fulminant and the measurable changes in metastases during the period of treatment were small compared with the striking changes in physical parameters.[12]

Site and type of the primary

There is paucity of literature data linking site and type of the primary malignant process and IFN toxicity.[12] In our series, mental deterioration and behavioral changes were observed in five patients with RCC treated by IFN-α.[12] None of our 46 melanoma patients showed any neurobehavioral disturbance.[13]

In another series, nine patients with leptomeningeal spread, of whom three had breast cancer, five malignant melanoma and the remainder had large cell lung cancer and lymphoma, developed neurotoxicity after intraventricular administration of IFN-α.[2]

When IFN-α was injected systemically neurotoxic signs and symptoms occurred in six patients with RCC, five with chronic myelogenous leukemia (CML), two with MM and one with breast cancer.[11] It should be noted that, as in our series, the majority of patients with solid primary tumor and neurotoxicity (six of nine) had RCC. The relation between RCC (and other primary tumors, but to a lesser extent) as a predisposing factor to the development of IFN-α related neurotoxicity is not clear. There was no relation between the sites of

metastases in our patients to the development and severity of the neurologic syndrome.[12]

Age, dose and schedule of treatment

For the same IFN-α doses, toxicity was the most severe when it was administered by continuous i.v. infusion over several weeks. By this way, a fairly low but constant IFN-α level allowed continuous effects on brain tissue. The least toxic way of administration was i.v. bolus, in which the highest, but more transient IFN-α level was evident in the serum.[1] Intramuscular or subcutaneous injections resulted in great persistence of IFN-α in the serum.[1]

The incidence of IFN toxicity on the central nervous system is related to the dose and the age of the patients.[4] In our study[12] the more severe symptoms occurred in older patients and within a shorter interval after the introduction of IFN treatment. The median age of our patients was 69 years, which is higher than in the other series.[5,9]

There was a strong correlation between the dose and schedule of IFN treatment and the severity of neurotoxic manifestations.[11]

In the study of Meyers *et al.*, the mean age was 55 years (range 28–61). The IFN dose varied from 3 to 10 million units daily or triweekly by systemic administration, according to different malignancies and schedules. Mean time of IFN treatment was 55 weeks (range 6–156 weeks). Six patients were treated for at least 1 year, and the others 40 days to 8.5 months before the development of neurologic signs.[11]

IFN-α, 3–9 × 10^6 units, three times a week, was administered intraventricularly through a right ventricular reservoir. Severe neurotoxicity was observed in seven of the nine patients. The median age of patients treated in this way was 45 years,[2] i.e. much younger than those who were treated by systemic injection.

Duration of the treatment

The duration of the IFN treatment was not strongly related to neurotoxicity.[11,12] One patient with lung metastases of RCC was treated by IFN-α, 9 × 10^6 units, three times per week, for more than 42 months, and four patients with metastatic MM were treated with the same schedule of IFN-α (but in combination with dacarbazine 400–800 mg/m^2 every 3 weeks) for periods of 16–52 months without developing this syndrome.

Ancillary workup: CSF analysis, neuroimaging and electroencephalogram (EEG)

CSF analysis in all of our patients was normal.[12]

CT findings in our patients included atrophy in two patients and periventricular lucencies in two patients. None of these were typical of IFN toxicity.[12] Linear measurements of the CSF spaces, including ventricular score, sulcal score, bifrontal and bicaudate cerebreventricular indices, were performed.[12] The values obtained in ventricular score and sulcal score did not relate to the mental state of the patients. The fact that significantly smaller ventricles were found in the more severely demented patients supports the hypothesis of neurotoxicity of IFN rather than structural changes in the brain.[12] Other authors also reported severe atrophy out of proportion to the patients' age in five out of 10 evaluated patients.[11] White matter changes were evident in three patients.

EEG studies demonstrated a generalized increase in slow wave activity which returned to normal after cessation of therapy.[1,11] Eighty percent of the patients had evidence of frontal and central synchronous delta and theta activity with occasional sharp components.[2]

Reduction of toxicity

Neurotoxicity of IFN-α may be reduced following dose modification in symptomatic patients.[1] Our recommendation is cessation of treatment in the more severe cases in order to avoid irreversible injuries.[12] Changing the route of administration may also reduce undesirable effects. It is worth noting that IFN-α may be less toxic when given in the early part of the night (10–12 p.m.) rather than in the morning.[1]

Conclusion

Neurotoxicity related to treatment with IFN-α is not rare; however, severe cases with a fatal outcome are still relatively infrequent, being observed in 7% of treated patients. IFN-α related neurotoxicity seems to be more common in the following

situations:

(i) Elderly patients.
(ii) Intramuscular or intraventricular administration.
(iii) Higher doses of IFN-α.
(iv) Frequent injections of IFN-α.
(v) Primary renal cell carcinoma.

Behavioral and mental changes in patients treated with IFN are warning signs and treatment should be withdrawn in the more severe cases.

References

1. Bocci V. Central nervous system toxicity of interferons and other cytokines. *J Biol Regul Homeos Agents* 1988; **2**: 107–18.
2. Meyers CA, Obbens EAMT, Scheibel RS, *et al.* Neurotoxicity of intraventricularly administered alpha-interferon for leptomeningeal spread. *Cancer* 1991; **68**: 88–92.
3. Blalock JE, Smith EM. Human leukocytes interferon: potent endorphin-like opioid activity. *Biochem Biophys Res Commun* 1981; **101**: 472–78.
4. Spiegel RJ. The alpha interferons: clinical overview. *Semin Oncol* 1987; **14** (suppl 2): 1–12.
5. Adams S, Quesada JR, Guttermann JU. Neuropsychiatric manifestations of human leukocyte interferon therapy in patients with cancer. *J Am Med Ass* 1984; **252**: 938–41.
6. Smedley H, Katrah M, Sikora K, *et al.* Neurological effects of recombinant human interferon. *Br J Med* 1983; **286**: 262–4.
7. Rohatiner AZS, Prior PF, Burton AC, *et al.* Central nervous system toxicity of interferon. *Br J Cancer* 1983; **47**: 419–22.
8. Mannering GJ, Deloria LB. The pharmacology and toxicology of the interferons. An overview. *Annu Rev Pharmacol Toxicol* 1986; **26**: 455–515.
9. Renault PF, Hoofnagle JH, Park Y, *et al.* Psychiatric complications of longterm interferon alpha therapy. *Arch Intern Med* 1984; **147**: 1577–80.
10. Merimsky O, Nisipeanu P, Loewenstein A, *et al.* Interferon-related cortical blindness. *Cancer Chemother Pharmacol* 1992; **29**: 329–30.
11. Meyers CA, Scheibel RS, Forman AD. Persistent neurotoxicity of systemically administered interferon-alpha. *Neurology* 1991; **41**: 672–6.
12. Merimsky O, Reider-Groswasser I, Inbar M, *et al.* Interferon related mental deterioration and behavioral changes in patients with renal cell carcinoma. *Eur J Cancer* 1990; **26**: 596–600.
13. Merimsky O, Chaitchik S. Our experience with α-interferon: metastatic malignant melanoma. *J Mol Biother* 1992; **4**: 135–8.

(Received 7 July 1992; revised version received 3 September 1992; accepted 14 September 1992)