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Original Article

Management of CNS toxicity of chemotherapy and targeted agents: 2020

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Abstract: Cancer treatment has evolved significantly over the last two decades. With the advent of targeted therapy, immunotherapy and immunotherapeutic agents conjugated to toxins, the spectrum of side effects has increased. This work is a compilation of side effects on the central nervous system due to various chemotherapeutic and immunotherapy agents followed by their recommended management.

Keywords: Intrathecal (IT), posterior reversible encephalopathy syndrome (PRES), central nervous system (CNS)

Introduction

Over the last two decades advances in knowledge in cancer pathophysiology, as well as molecular basis of disease have translated into multiple advancements in therapy approach. While many of the classical or traditional chemotherapeutic agents are still in use and have been well studied, including their side effects and neurotoxicity profile, new drug categories have been developed. Prolonged survival of patients has made neurotoxic effects of the newer targeted or immunotherapeutic agents which are now being studied often with central nervous system (CNS) manifestations which were not equally evident when patient had shorter overall survival [1]. CNS manifestations may be irreversible and/or slow to manifest. For this reason changes must be assessed and documented establishing a temporal association between initiation of treatment, time to evidence of signs/symptoms and underlying possibly confounding comorbidities. It is important to recognize these changes early in their presentation as although challenging, it is critical to distinguish between disease, paraneoplasia or an already established chronic neurological comorbidity. The latter case may not need change in dose or discontinuing the medication.

The ease with which an agent crosses the blood brain barrier is associated with the effects to the CNS. Other risk factors for drug-induced CNS toxicity are combination of therapies and prior brain irradiation although genetic factors have also been proposed [2]. Inherited polymorphisms in the CEP27 gene has been proposed as a risk factor for developing vincristine-induced neuropathy. Although peripheral neuropathy is discussed, it also correlates with the possibility of genetic risk factors in CNS toxicity [3]. It has been proposed that the acute toxicity to the CNS is the result from excitatory mechanisms and apoptotic cell death after treatment with cisplatin, cytarabine, cyclophosphamide, methotrexate, fluorouracil, vinblastine among others [4]. These agents are believed to increase the blood-brain barrier permeability increasing the risk for CNS toxicity. Chemotherapy agents and targeted agents with significant CNS toxicity profile are listed in **Tables 1** and **2**.

Discussion

There is a plethora of neurotoxic effects caused by classical/traditional and newer targeted groups of anti-cancer agents. It is critical to monitor closely any neurologic change that may suggest a sign of neurotoxicity, as this is key in the prevention of permanent neurological dam-

Table 1. List of chemotherapy agents which cause CNS toxicity

Agent	CNS Effect	Management
Cisplatin	Encephalopathy/Seizures/PRES	• Encephalopathy/PRES - D/C agent • Seizures - anti-epileptics
Busulfan (high dose)	Seizures	• Prophylactic anti-epileptics
Cytosine arabinose	Cerebellar syndrome/Seizures	• Cerebellar syndrome - D/C agent • Seizures - anti-epileptic
L-asparaginase	Encephalopathy/Seizures	• Encephalopathy - D/C agent • Seizures - anti-epileptics
Methrotrexate (mostly high dose)	Aseptic meningitis (IT)/Acute & Subacute Encephalopathy/Seizures/Leukoencephalopathy/PRES	• Aseptic meningitis/acute & subacute encephalopathy - usually self-limited • Seizures - anti-epileptics • Leukoencephalopathy - often self-limited • PRES - D/C agent, blood pressure control, supportive [5]
Nitrosoureas	Encephalopathy/Seizures	• Seizures - antiepileptics
Vincristine	Seizures/Coma/Cranial nerve mononeuropathies (oculomotor most common) [6]	• Dosage modification or D/C
Cytarabine (high dose)	Encephalopathy/Aseptic meningitis (IT)/Cerebellar toxicity/Seizures/PRES	• Encephalopathy/Cerebellar toxicity - D/C agent • Seizures - anti-epileptics • PRES - D/C agent, blood pressure control, supportive [5]
Cyclosporine	PRES	• D/C agent, blood pressure control, supportive [5]
Cyclophosphamide	PRES	• D/C agent, blood pressure control, supportive [5]
Gemcitabine	PRES	• D/C agent, blood pressure control, supportive [5]
Paclitaxel	PRES	• D/C agent, blood pressure control, supportive [5]
Ifosfamide (higher incidence with high-dose)	Encephalopathy/Seizures	• Usually self-limited/Methylene blue [7] • Seizures - anti-epileptics
Interferon (high dose)	Encephalopathy/Cerebellar dysfunction	• D/C agent
Bortezomib	PRES	• D/C agent, blood pressure control, supportive [5]
Thalidomide	Acute encephalopathy	• Self-limited

age. Although there is a vast array of peripheral neurological effects, we discuss effects to the central nervous system. Some treatments carry precautions of interactions with other medications. Such is the case of high-dose methotrexate where concomitant use of phenytoin, aspirin, sulfonamides, tetracyclines and other protein-bound medications. They can displace methotrexate causing an increase in circulating free drug and higher risk of neurotoxicity. Proton pump inhibitors (PPI) can also interact with high-dose methotrexate elevating and prolonging circulating levels increasing the risk of neurotoxicity [9]. Clinical presentation of CNS toxicity can range from headache which may or may not be a result of aseptic meningitis (common with intrathecal nonspecific or targeted therapies). The patient can present with sei-

Table 2. List of targeted agents which cause CNS toxicity

Agent	CNS effect	Management
Sorafenib (RAF-kinase inhibitor)	PRES	• D/C agent, blood pressure control, supportive [5]
Sunitinib (TKI)	PRES	• D/C agent, blood pressure control, supportive [5]
Ipilimumab	Aseptic meningitis	• D/C agent
Rituximab	Headache/PRES	• PRES - D/C agent, blood pressure control, supportive [5]
Axicabtagene Ciloleucel [8]	Encephalopathy/Seizures	• Prophylactic anti-epileptics • Therapeutic combination of anti-epileptic agents and steroids

zures convulsive or non-convulsive (in case of underlying encephalopathy with status epilepticus). Seizures can also result from interferon and interleukin-2 which cause the release of cytokines as seen in CAR T-cell therapy. However seizures is the most common presenting symptom of posterior reversible encephalopathy (PRES) [5]. PRES can be secondary to treatment-induced hypertension therefore blood pressure control should be addressed. Although PRES is more common after cyclosporine and cyclophosphamide, several anti-cancer agents can cause PRES [5].

Encephalopathy can present with altered mental status, confusion, somnolence, seizures, stupor. This in many cases is reversible as it improves after discontinuing the anti-cancer agent. Of note some patients develop decreased cognition after being submitted to chemotherapy regimens, this the concept of "chemobrain". Although in some cases can be reversible, many patients develop structural neurological damage evident on brain imaging and is usually permanent [5]. An important consideration in patients treated with immunosuppressive agents and who are presenting chronic mental status changes is progressive multifocal leukoencephalopathy (PML) as underlying etiology. Management for PML is geared toward recovery of the immune system discontinuing the anti-cancer agents.

As neurologic clinical presentation may result from indirect effect, several medications favor hypercoagulable conditions and increase the risk of stroke. Some of these medications are L-asparaginase (with higher risk of venous sinus thrombosis), doxorubicin, methotrexate and platinum-based treatments which also carry cerebrovascular event risk. Another consequence of CNS toxicity is cerebellar dysfunction which may be associated with high dose cytarabine, 5-fluorouracil, vincristine, oxaliplatin. Clinical evaluation should examine for nystagmus, scanning speech. Usually symptoms are reversible, resolving after discontinuation of agent [5].

Movement disorders are not necessarily an effect of chemotherapy. However they may result from anti-emetic medications and their antagonism to dopamine receptors as well as chemotherapeutic agents such as interferon-alpha, steroids and vincristine [5]. Dystonic reactions to anti-emetics can be managed with anti-cholinergics, however if anti-emetic treatment is prolonged, this may result in symptoms of akathisia and parkinsonism both which usually resolve after discontinuing the medication. Anti-emetics with mechanism of action antagonizing serotonin receptors are less likely to result in movement disorders or extra-pyramidal symptoms [5].

Conclusions

As more advanced and specific anti-cancer treatments become available, monitoring of neurologic signs and symptoms is increasingly critical for prevention of permanent damage and management of reversible changes. Many of the symptoms will require discontinuing the offending agent, however certain symptoms may be treated medically until the underlying etiology resolves or becomes self-limiting. Neurotoxicity associated with chemotherapy often times result in dose-limiting toxicity. It is important to recognize the different common neurologic manifestations for timely decision making, implementing adequate therapeutic interventions for high value care.

Disclosure of conflict of interest

None.

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References

[1] Armstrong T and Gilbert MR. Central nervous system toxicity from cancer treatment. Curr Oncol Rep 2004; 6: 11-19.

[2] Cavaletti G, Alberti P and Marmiroli P. Chemotherapy-induced peripheral neurotoxicity in the era of pharmacogenomics. Lancet Oncol 2011; 12: 1151-1161.

[3] Diouf B, Crews KR, Lew G, Pei D, Cheng C, Bao J, Zheng JJ, Yang W, Fan Y, Wheeler HE, Wing C, Delaney SM, Komatsu M, Paugh SW, McCorkle JR, Lu X, Winick NJ, Carroll WL, Loh ML, Hunger SP, Devidas M, Pui CH, Dolan ME, Relling MV and Evans WE. Association of an inherited genetic variant with vincristine-related peripheral neuropathy in children with acute lymphoblastic leukemia. JAMA 2015; 313: 815-823.

[4] Soussain C, Ricard D, Fike JR, Mazeron JJ, Psimaras D and Delattre JY. CNS complications of radiotherapy and chemotherapy. Lancet 2009; 374: 1639-1651.

[5] Stone JB and DeAngelis LM. Cancer-treatment-induced neurotoxicity--focus on newer treatments. Nat Rev Clin Oncol 2016; 13: 92-105.

[6] DeAngelis LM PJ. Side effects of chemotherapy. Neurologic Complications of Cancer. 2nd edition. New York: Oxford University Press; 2009. pp. 447.

[7] Pelgrims J, De Vos F, Van den Brande J, Schrijvers D, Prove A and Vermorken JB. Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. Br J Cancer 2000; 82: 291-294.

[8] Chu E and DeVita VT Jr. Physician's, cancer chemotherapy drug manual, in Physician's, cancer chemotherapy drug manual. Jones & Bartlett Learning: Burlington, MA. 2020. pp. 51-53.

[9] Khleif SN and Skeel RT. Side effects of chemotherapy, in skeel's handbook of cancer. Lippincott Williams & Wilkins Philadelphia. 2016. pp. 632-655.