



Neurotoxicity Associated with Cancer Treatment

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Cancer is one of the prevalent medical problems among people especially in more developed and industrialized population. Now a day, it is considered as the third leading cause of death following cardiovascular problems and accidents. Moreover, the therapeutic approach to malignant tumors has been developed significantly compared with 70s and 80s. Many immunotherapies and targeted therapies have been developed and approved for both solid tumors and hematologic malignancies. Curable approach has been available for many deadly malignancies and multiple treatment lines have been proposed and validated based on the clinical trials in the majority of cancers. Innovative technologies such as nanotechnology have been proposed and developed to optimize the bioavailability of the therapeutic agents within the tumor. However, adverse events associated with these novel therapeutic approaches have been inevitable. Many of these adverse events present acutely during or shortly after the completion of the chemotherapy and resolve spontaneously or with short term palliative approach or even reducing the dose and schedule of the chemotherapy protocol. Few adverse events however, might last for longer periods of time and even life long and show a significantly negative impact on the patients' quality of life despite the application of palliative approach. Although availability of multiple combination chemotherapy protocols and variety in the type of therapeutic approach might play a role in reducing these adverse events, it is not able to completely eliminate these unwanted effects. Besides, relapsing nature of cancers that necessitates multiple lines of treatment lead to additive and sometimes synergic adverse events that might further debilitate the patients.

Chemotherapy associated neurotoxicity is one of these adverse effects of cancer treatment that has a long history. Vinca alkaloids, such as vincristine and vinblastine, as well as platinum compounds, namely cisplatin and carboplatin are among the oldest chemotherapeutic agents that has been introduced and served in cancer treatment since 50s and 60s. Taxanes are another group of chemotherapeutic agents with potential neurotoxicity that in spite of their later development, have gained multiple therapeutic indications among different types of solid tumors. Neurological adverse events are not limited to chemotherapeutic agents. Newer generations of targeted therapies and even antibody-drug conjugate innovative medications have also shown neurological adverse events. Imids, such as thalidomide and lenalidomide (Revelmide) and proteasome inhibitors, such as bortezomib (Velcade) are the prototypes of targeted therapies with prominent neurotoxicity as adverse events. Even blinatumomab, a CD 19 targeting monoclonal antibody that has gained approval for treatment of acute lymphoblastic leukemia has been associated with neurotoxicity, presenting as seizure and leukoencephalopathy.

Neurotoxicity associated with cancer treatment modalities has a wide spectrum not only in clinical presentation, signs and symptoms, but regarding the natural history, prognosis and proposed efficient therapeutic modalities. Neuropsychiatric problems, such as somnolence, mood changes and depression and even organic focal CNS abnormalities are the other side of this neurotoxicity spectrum that might be indistinguishable from signs and symptoms associated with the cancer itself or psychological reactions of the patients to the potentially deadly diagnosis [1-3].

Incidence and prevalence of chemotherapy induced neurotoxicity is difficult to estimate. Neuropsychiatric symptoms might be referred to other causes, such as primary cancer itself or other medications that are taken concurrently by the patients. However, peripheral neuropathy as one the most prominently encountered adverse event has been reported in up to 68% of patients who have received neurotoxic



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chemotherapeutic agents. Symptoms of chemotherapy associated neuropathy might become chronic in about 30% of these patients, respectively [4-6].

From clinical point of view, neurotoxicity of chemotherapeutic agents might be divided into two main categories of peripheral and central nervous neurotoxicity. Peripheral neuropathy may present as either sensory or motor or even a combination of both sensory and motor neuropathy. Signs and symptoms of central nervous system neurotoxicity on the other hand are less defined compared to peripheral neuropathies. They might present as common cancer associated symptoms, such as somnolence, mood changes, depression and even seizure to more complicated scenarios such as focal neurologic deficits, and leukoencephalopathies. Peripheral neuropathy of sensory type is by far the most frustrating feature of cancer associated neurotoxicity with a negative impact on patients' quality of life. Type of involvement is correlated to the type of the chemotherapeutic agent. However, sensory symptoms such as tingling, burning sensation and dysesthesia are common. Proprioception, vibration, light touch and position are generally impaired with devastating consequences. Motor and even autonomic involvement might also present in severe cases.

Different mechanisms have been proposed for chemotherapy associated neurotoxicity based on the type of the responsible chemotherapeutic agent. Vinca alkaloids, and taxanes mainly inhibit microtubule formation and proteasome inhibitor bortezomib shows tubular toxicity, hence, interfering with neuron energy delivery mechanisms leading to neurotoxicity. Platinum compounds generally damage the dorsal root ganglia (DRG) due to its vulnerability and lack of efficient blood-nerve barrier. Other possible explanations are vascular damage of peripheral nerves. In general, larger peripheral nerves are involved and small nerves are spared. However, these mechanisms are not specific to the type of chemotherapeutic agent and more than one mechanism is usually involved for each specific type of the drug [7-10].

Central nervous system associated toxicity, on the other hand has also been reported with different type of chemotherapeutic agents, such as ifosfamide, cytarabine, methotrexate, 5-FU and even therapeutic cytokines such as interferon alfa and interleukin-2. ⁽¹¹⁾ Multiple mechanisms and pathogenesis has been suggested and observed for this type of neurotoxicity, such as chemotherapy associated direct toxicity to myelin, vascular endothelial damage, and even thrombotic microangiopathy. Alteration in thiamine due to the chemotherapeutic agents itself or its metabolites has also been suggested in specific type of chemotherapeutic agents, such as ifosfamide [11-15]. Apart from type of the chemotherapeutic agent and dose and schedule of treatment modality, other factors, such as kidney and liver function, past history of radiation to CNS or co administration of other medications such as immunosuppressive therapy may also play a role in presence, severity and even the outcome of the neurotoxicity. Other important factors that have been suggested to play a role are the genetic polymorphisms in folate metabolizing enzymes and apolipoprotein E, as well as in the blood-brain barrier transporter genes. Leukoencephalopathy, meningitis (especially associated with intrathecal administration of chemotherapeutic agents), cerebellar dysfunction, myelitis, visual

or hearing impairment, ataxia and seizure, as well as psychiatric presentations such as mood changes, sleep pattern changes, or even depression has been reported as clinical presentations in CNS neurotoxicity. Interestingly, despite the systemic nature of exposure to neurotoxic substance, focal neurologic symptoms are not uncommon [12, 16,17].

Apart from few chemotherapeutic agents with known antidotes that reverse their toxicity such as methotrexate, approaching neurotoxicity associated with many chemotherapeutic agents follows identical steps, early detection of clinical signs and symptoms, co morbidities that might potentiate these toxicities, such as renal and liver dysfunction, reducing the exposure by changing the treatment protocol and dose- schedule of treatment if possible, palliative managements, as well as anti-inflammatory treatments such as corticosteroids, COX-2 inhibitors, anti-aggregation and even anticoagulants especially when thrombotic microangiopathy is suspected. The prognosis however, is largely dependent on the causative agents and the extent of damage.

From therapeutic point of view, no specific modality has been proven to resolve the signs and symptoms or even play a preventive role for both central and peripheral nervous system toxicities associated with chemotherapy. However, several classifications of treatments have been proposed and tried. Antioxidants, such as acetyl L-Carnitine, glutathione, glutamine, vitamin B derivatives such as vitamin B6 and B12, as well as fish oil have been proposed for peripheral nerve toxicities associated with platinum compounds, taxanes and even bortezomib. Anti-convulsants are another classification of therapeutic agents that has been suggested mostly as a symptomatic management for sensory neuropathy associated symptoms such as dysesthesia, tingling and burning. Carbamazepine, ethosuximide and newer generations of this group of treatment modalities such as gabapentin and pregabalin has also been administered and tried in clinical trial setting. Anti-depressants, such as amitriptyline and duloxetine have also been tried in clinical setting to control neuropath associated symptoms. Analgesics and anti-inflammatory drugs, such as COX-2 inhibitors, corticosteroids, opioid analgesics have been tried in clinical trial setting addressing symptomatic management of chemotherapy associated peripheral neuropathy. Interestingly, cannabinoids are another group of therapeutic modalities that has been proposed and tried in clinical setting based on their ability to control neurologic complications of chronic degenerative disorders such as multiple sclerosis. Among all the mentioned medications that has been proposed and applied in clinical trials, none of them has shown protective role against chemotherapy associated peripheral neuropathy. Moreover, only duloxetine has shown therapeutic effect to control taxane associated peripheral neuropathy in phase III clinical trials [18-20].

A variety of non-pharmacological modalities has also been proposed and tried in clinical setting of chemotherapy associated peripheral neurotoxicity. Acupuncture has been the most widely applied treatment by far. It has shown efficacy in limited clinical trials, however, its efficacy in neurotoxicity associated with different types of chemotherapeutic agents needs to be further evaluated in clinical trial settings [21].



In conclusion, despite the significant progresses in both chemotherapeutic approaches and targeted therapies in solid tumors and hematologic malignancies, palliative management of the adverse events associated with treatment and the disease itself is still one of the unmet clinical needs in cancer patients. Although many cancers are still considered as the incurable diseases with a limited survival chance, the list of curable cancers is fortunately growing further. Moreover, availability of multiple lines of treatment for each cancer type increases the overall survival of the cancer patients. These progressions necessitate more attention to be paid to the signs and symptoms brought by the cancer itself or therapeutic approaches. Among all of the signs and the symptoms associated with cancer and its treatment, neurotoxicity is one of the mostly encountered and long lasting symptoms that need special attention due to its negative impact in quality of life. Both preventive and therapeutic approaches to this adverse event need to be addressed further in large randomised clinical trial setting.

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