

Cancer Therapy and Neuromuscular Complications: A Mini Review

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Abstract

Neuromuscular complications can be caused by all types of interventions, various mechanisms and occur and as acute, chronic or late effects. The most frequent causes of lesions are toxic, either by radiotherapy (RT) or chemotherapy. Increasingly neurotoxicity is a dose limiting factor in tumor treatment.

This mini review is based on a structured review in the JNS article [1], followed by a more detailed analysis of chemotherapy induced neuropathy (CIPN) [2].

The aim of this mini review is to comment on recent developments. These are the increasing number of late effects in cancer survivors, the immune mediated neuromuscular effects and the need for specific pain treatment and the need for onco-rehabilitation.

Keywords: *Neuromuscular Complications; Cancer; Late Effects; Immune Mediated; Pain; Onco-Rehabilitation*

Introduction

The non-neurological complications of cancer treatment as nausea, haematotoxicity, bone marrow suppression are increasingly well managed. However neurological effects as neurotoxicity caused by RT, and of drug treatment are a becoming a dose limiting factors and in addition, also the increased number of long term survivors demonstrates, that persisting neurological symptoms may have been underestimated. Late effects become an issue, as they have an influence on the quality of life (QL).

Toxicity is usually a mechanistic approach. A drug given in a certain quantity to a person, will cause toxicity in an expected dose relationship. This is in generally correct but practically individuals have different susceptibilities. Moreover some drugs can exert an immediate toxicity as oxaliplatin. Another mechanism is that some biological drugs cause autoimmune diseases. These can be severely debilitating and must be distinguished from toxicity.

Onco- rehabilitation is an emerging topic and increasingly also lesions of the peripheral nervous system are a concern of rehabilitation. Rehabilitation cannot be confined towards pain treatment and improvement of motor and sensory symptoms, but must include the improvement of function and activity of daily life. Pain treatment is usually complex and for this comment the focus is on neuropathic pain only, which is only and aspect of cancer pain [3,4].

Methods

The paper written in the JNS [1] is a systematic approach towards the individual parts of the peripheral nervous system and the different types of mechanisms ranging from neoplastic, immune mediated, paraneoplastic, toxic and others. Although the JNS paper is quite comprehensive and will be used as the basis of this mini - review; several recently and new emerging issues will be discussed subse-

quently. These are late effects of treatment, humoral effects, immune mediated effects and the increased need for rehabilitation and pain management.

Late effects

Treatment of cancer is becoming more frequent, and also more efficient. Thus the number of survivors increases steadily. In particular in childhood cancer several observations, concerning the late effects have been made [5].

Neuropathy

In peripheral neuropathy in particular younger adults with curable cancer (e.g. seminoma) a number of late effects, which in addition to cumulative effects [6] impair ADL and QL. Increasingly the late effects attract attention as the number of long time surviving patients increases due to better cancer management. There are several limitations in prevention and treatment of classical CIPN [7]. In addition to medical strategies and procedures also self-management [8] has become an issue.

The main symptoms concerning these patients are: persisting sensory symptoms, deficits in fine motor tasks ("clumsiness"), neuropathic pain and Raynaud's syndrome.

Radiotherapy

Radiation effects on the nervous system are well known. Conventionally early, early - delayed and late RT complication are described in the nervous system. However not only the peripheral nervous system (PNS) alone, but also fibrous structures, fasciae damaged by RT can cause additional symptoms. This has been summarized in the term "Radiation fibrosis syndrome" [9-12]. Although many studies have focused on the late effects of radiation of the nerve plexus, little is reported on the late RT effects on individual peripheral nerves [12,13].

Examples of complex damage have been described after mantle field radiation in Hodgkin's disease [14]. However in individual cases it is difficult to distinguish between myelopathy, nerve damage, myopathy [15] and fibrosis of connective tissue and combinations thereof. In regard to swallowing difficulties, additional damage to the esophagus and surrounding tissue is suspected [11,16] in patients after mantle field RT.

Prior radiation of muscles can also induce a RT induced myositis and the radiation recall syndrome [17].

Contrary to the previous assumption that muscle tissue is RT resistant, this is unlikely [11]. Functional decline, fibrosis and reduced range of motion can be expected, after RT.

Attention also needs to be directed towards the muscle metabolism in cancer [18]. This is important as sarcopenia and also cachexia seem to be a prognostic factor for survival. One of the future goals will be the prevention or treatment for cancer cachexia.

In particular in elderly patients cachexia contributes towards frailty which predisposes for falls. Cancer cachexia presents in 3 stages: pre-cachexia, cachexia, and refractory cachexia [19]. The importance to prevent cancer cachexia is emerging and several trials have been initiated [20,21], and early interventions will be needed.

Hormonal effects

The most common side effect of hormonal treatment is steroid myopathy [22]. It is uncertain if this condition is reversible and what long term effects on muscle can be expected. Tamoxifen treatment can be associated with carpal tunnel syndrome [23].

Despite the frequency of treatment, the effect of long term androgen therapy and muscle function is a neglected topic. Men with prostate cancer often receive anti-androgenic therapy which reduces muscle bulk and strength [18]. Vice versa hormone replacement therapy with androgens may also have an effect on muscles [24].

Immune therapy effects

Neuropathies can be caused by interferons IFN- α [25]. Also an autoimmune mechanisms for ganglionitis [26] and small fiber neuropathies has been proposed [27].

Various types of immune therapies are used effectively for the treatment of cancer and can be related with autoimmune diseases affecting the PNS [28].

Increasingly reports on neuropathies [29-31] and muscle involvement [32], and rhabdomyolysis appear in immune check point inhibitors as ipilimumab, and nivolumab and others which emerge increasingly [33].

Also myasthenia gravis can be induced [34], or exacerbated [35,36] by immune check point inhibitors.

The present spectrum of immune check point inhibitor induced neuromuscular syndromes is based on many individual observations and cause immune mediated PNS disease, or exacerbate existing diseases as MG. This new spectrum will increase due to increased clinical use, as well as an increasing number of new drugs.

These side effects do not qualify as classical neurotoxicity, but can be considered as a bystander effect of immune treatment and open a new category of side effects.

It can be assumed that also other drugs can be considered to induce neuropathy, which cannot be attributed to the classical toxicity model, which is mostly based on a toxic cumulative dose. As for instance Ibrutinib, which acts as a Bruton tyrosine kinase inhibitor [37], induces a sensory neuropathy, which is unexpected for this compound.

For CIPN it has been suggested that in CIPN an inflammatory response [38] could be elicited which could kindle the persistence and progression of CIPN. These considerations will be the basis of studies to use IVIG, and also possibly bortezomib to reduce a possible inflammatory response.

Onco Rehabilitation

The issue of rehabilitation in cancer patients is attracting [39-41] attention. Barriers to ban oncological patients from rehabilitation have to be still overcome [42]. Neuromuscular targets of rehabilitation are sensory, motor dysfunction and neuropathic pain. Long term effects are clumsiness, dyscoordination, falls and reduced mobility. Electrophysiological testing can be helpful not only for diagnosis but for the evaluation of the extent of damaged structures of the PNS.

Effects on long term survivors show gait abnormalities in children [43], and long term studies up to 6 years in women with CIDP show increased falls [44].

The efforts of rehabilitation need to be directed to achieve independence and reduce symptoms. This is not confined to neuropathic symptoms, but also includes the maintenance of independence, posture and balance [45] and the avoidance of frailty. Long term effects in CIPN also include Raynaud syndrome and autonomic symptoms [46].

Pain

Cancer pain is an important issue [4,47], and for the neuromuscular system a more specific approach is necessary. Individual pain syndromes are the breast mastectomy pain complex [48], neuropathic pain syndromes in lesions of the nerve plexus, local pain syndromes as caused by osteoporosis, and also more rare issues as jaw pain [49] and dentalgia [50] are within the spectrum of neuropathic pain. Rarely pruritus as an equivalent of neuropathic pain can appear and needs specific treatment [51].

Rarely phantom pain after amputation of the breast, rectum, eye and limbs occurs and needs specific pain approaches.

Hopefully the current concern on the distribution of opioids will not threaten the support of cancer patients with opioid analgesics.

Conclusion

The incidence of cancer is increasing. Modern therapies are effective and the increased number of cancer survivors provide a number of new issues in patients with cancer suffering from neuromuscular symptoms. Our survey in the JNS [1] allows a systematic approach to neuromuscular symptoms in this patient group.

In neuromuscular disease similar symptoms can be caused by different mechanisms, which may require different treatment strategies.

A new category of neuromuscular effects appears due to immune therapy, in particular immune check point inhibitors. These are not toxic effects per se, but induce immune mediated neuromuscular syndromes.

Additional attention is needed for late and persisting effects in long term survivors, the immune mediated side effects and neurorehabilitation and specific pain treatment for neuropathic pain

Conflict of Interest

There is no conflict of interest.

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