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EDITORIAL

Elapsed time for an unresolved adverse event: systemic anticancer therapy-induced neurotoxicity calls for action

In recent years, we have seen an acceleration of new discoveries in cancer treatment leading to longer life expectancy, even in hard-to-treat malignancies. Older chemotherapeutic agents coupled with newer drugs with different mechanisms of action are not only more effective, but unfortunately could also synergistically multiply some side-effects.

Among others, neurotoxicity remains a major issue, affecting the dose intensity of therapeutic agents and worsening quality of life for patients.[1] Despite many published papers, guidelines, and expert opinions, central and peripheral neurotoxicity induced by anticancer treatments still remain unsolved challenges.

In this issue of the *Annals of Oncology*, ESMO—EONS—EANO[2] report a joint effort to produce timely, updated guidelines that summarize the methodological limitations demonstrated in clinical trials to prevent or treat this adverse event. Some critical points should be emphasized: as every phenomenon in medicine must be quantified, predicted, and then treated, so also the peripheral and central neurotoxicities induced by systemic anticancer therapy deserve such attention.

Good diagnostic screening and evaluation have to be offered to all patients that receive potentially neurotoxic anticancer treatments, keeping in mind that electrophysiological tests could predict chemotherapy-induced peripheral neurotoxicity (CIPN), notwithstanding that they are not routinely employed in clinical practice.[3] Both the patient's history (e.g. pre-existing comorbidities) and type of anticancer treatment may identify patients more prone to this disabling adverse event; however, no single genetic polymorphism studied to date can stratify the risk of CIPN development.[4]

In recent years, more preventative than curative trials addressing neurotoxicity have been conducted.[5,6] Several weaknesses in these trials may be identified: the absence of predictive models to select higher-risk patients for prevention trials, lack of well-defined control groups, inconsistencies in outcome measures, and the issue of combining patients treated with various drugs, though having different mechanisms of action.

Considering the field of CIPN treatment, there is little evidence for pharmacological interventions (e.g. duloxetine). Often, patients are given confounding recommendations, even if there are no strong supporting data about drugs or non-pharmacological interventions. This increases the use in clinical practice of a wide number of "pharmacological supplements" without demonstrated efficacy, leading to frustration of patient expectancies and increased out-of-pocket expenses.

The drugs studied to date are examples of symptomatic actions aimed at mitigating neuropathic pain, numbness, or tingling. More research should be performed to apply knowledge of the mechanism of damage characteristic of each drug (e.g. taxanes, platinum derivatives) and to discover and test targeted agents capable of blocking or reversing the neurological derangement.[7-9] Recently, pursuing this pathway, there is experience in reprogramming human somatic stem cells into neurons, bypassing peripheral neurological death, thus restoring normal neurological cellular function.[10]

The field of central neurotoxicity is even more devoid of therapeutic approaches. Mostly, the levels of evidence given by the ESMO—EONS—EANO guidelines are "V", meaning that the recommendations derive from studies without control groups, case reports, or expert opinions. Central neurotoxicity represents a dramatic event for patients and treating physicians, and the lack of predictive factors as well as of efficacious therapies often gives a sense of helplessness in this regard.

Therefore, as oncologists, we may often feel as spectators of a movie, entering the cinema late and not being able to understand the movie's plot or comment on it. On the other hand, several trials are currently ongoing related to neurotoxicity prevention and treatment that could open new scenarios. We advocate the increase of prospective studies, whenever is possible, under the auspices of scientific groups involved in supportive care research.

Moreover, these trials should collect the patient's point of view, using validated tools like measures of patient-reported outcomes (PROs), with the aim of addressing both patient and physician perspectives. Unfortunately, the gap between mechanistic pathways of drugs inducing neurologic impairment and the rationales behind employing agents or devices to combat this adverse event continue to be reported in the literature. Sponsored clinical trials as well as academic investigator-initiated studies still demonstrate this flaw.[11] Awaiting better results, the updated guidelines continue to be useful as they indicate the way forward: building dedicated multidisciplinary teams, employing subjective and objective scales to measure and properly report neurotoxicity, and entering patients in clinical trials, thus avoiding the use of unrecommended drugs to tackle this troubling and disabling adverse event.

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