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RESEARCH ARTICLE

CHEMOTHERAPY NEUROTOXICITY: PHARMACOLOGICAL AND TOXICOLOGICAL ASPECTS

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ABSTRACT

Objective: The purpose of this article is, starting from pharmacological aspects, to evaluate the central and peripheral neurotoxicity of some chemotherapy compounds and also some possible neuroprotection strategies. **Methods**: both personal knowledge of pharmacology and the use of both paper books and international website databases such as pubmed, scopus, google scholar, researchgate were used to develop the article, typing in keywords such as "chemotherapy neurotoxicity" or "neurotoxicity" associated with specific compound names. **Results**: Chemotherapy-induced neurological complications, while overall rare and non-fatal, can be disabling and even lead to serious difficulties in grasping and manipulating objects or the inability to perform the most common daily gestures. The duration of these symptoms, although usually regressing in part between one treatment cycle and the next, is cumulative and, sometimes, the limiting factor for the tolerability of the therapy itself. Due to neuropathy, therapy must necessarily be reshaped or even stopped. **Conclusions**: chemotherapy-induced iatrogenic neuropathies remain rare overall, around 10-15% of treated subjects, but can be disabling. Early treatment and neuroprotection strategies are essential, such as supplementation with antioxidant and lipophilic substances such as vitamin derivatives or the use of systems to better convey the drug in tumor tissues, reducing systemic exposure and their side effects.

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INTRODUCTION

From cancer registries, in Italy every day about 1000 people are diagnosed with cancer, with over 360 thousand new cases per year. Fortunately, in many cases, thanks to early diagnosis and new therapies, a considerable part survives the disease, in particular in Italy there are over 3 million long-surviving subjects, with a past diagnosis of malignant tumor behind them. These numbers have led to the progressive development of new anticancer drugs that are increasingly effective and targeted at specific molecular targets. The first chemotherapy drugs developed date back to the "sulfonate mustards", so-called for the characteristic smell of mustard and used as a gas during the First World War by the Germans as chemical warfare agents. Chemotherapy drugs, not acting in an absolutely specific way on the tumor cell (which derives from the accumulation of genetic alterations of a cell of the self), have a low therapeutic index with consequent toxicity even to normal tissues with high proliferative activity such as bone marrow and mucous membranes. In particular, based on the time of onset, we classify immediate effects (within 24 hours of administration as extravasation necrosis, nausea, skin rash and anaphylactic reactions), early (within a few days or weeks as mucositis, cytopenias, alopecia, diarrhea), delayed (after weeks or months such as amenorrhea, azoospermia, pulmonary fibrosis and neurotoxicity) and late (may appear even after months or years such as alkylating-induced sterility or methotrexate-induced liver fibrosis)(2). Chronic toxicities are related to cumulative effects of multiple administrations and may not be fully reversible with drug withdrawal. For agents that cause irreversible chronic toxicities and are of great clinical relevance, threshold doses have been set such as anthracycline cardiomyopathy, where the total threshold dose not to be exceeded is 550 mg / m ^ 2 since for values greater than 600 the risk of cardiomyopathy is greater than 30%.

Chemotherapy neurotoxicity occurs in 15-20% of treated patients, which however are approximately 3,500,000 annually in the Western world, with compounds whose toxicity is dose-limiting for the central nervous system (CNS) and the peripheral (PNS). As with all iatrogenic toxicities, neurological toxicity also depends on the type of drug used, the cumulative dose, the routes of administration and any interference with other drugs taken, and the general condition of the patient. Neurotoxicity can be from direct damage to nerve cells or indirectly linked to drug-induced vascular or metabolic dysfunctions. Direct neurotoxic compounds are mainly antimitotics including vinca alkaloids, taxanes, etoposide, platinum derivatives, alkylating agents, and antimetabolites such as methotrexate, cytosine arabinoside, and 5-fluorouracil while monoclonal antibodies can give cross-reactivity and immunological reactions. Before describing in detail the mechanisms of toxicity, the main characteristics of the compounds most often associated with neurological phenomena will be briefly described (1,2).

CHEMOTHERAPY NEUROTOXICITY: PATHOGENETIC TYPES AND MECHANISMS

In general, neurological complications from chemotherapy can affect (5):

●The central nervous system (CNS) with acute encephalopathy, one of the most frequent side effects and can be caused by a large variety of drugs administered intravenously (iv) and intrathecal (it). The lesions involve the white matter of the posterior regions, sometimes the gray, and are usually reversible. Drugs such as methotrexate and cyclosporine, on the other hand, cause damage to the deep cerebral and cerebellar white matter with similar acute and reversible symptoms. Chronic encephalopathy is generally caused by the association of chemotherapy with radiotherapy of the brain and assumes the characteristics of a "subcortical dementia" that is highly variable in severity and latency concerning the treatment. Methotrexate is among the most frequently involved drugs (1,5). Another central complication described as chemo neurotoxicity is PRES (posterior reversible encephalopathy), with impaired upper cortical functions, headache, nausea/vomiting, aphasia, apraxia, and altered consciousness, and where MRI shows areas of demyelination of the substance white parieto-occipital bilaterally symmetrically.

●The peripheral nervous system (SNP) with potentially disabling damage whose prevalence is 3-7% in patients treated with a single drug and 38% in those undergoing multiple drug therapy. The predisposition to manifest symptoms of peripheral distress is greater in patients who have previously contracted a disease of the PNS, or have been subjected to neurotoxic treatments or still, are carriers of even sub-clinical neuropathies from different causes such as diabetes and alcohol. It occurs due to damage to the dorsal root ganglia with axonal involvement and manifests itself with paresthesia, dysesthesia, numbness of the extremities in a symmetrical way up to, in the most severe cases, a loss of proprioception and tendon reflexes. Platinum derivatives can cause neuronopathy, ie diseases of the sensory neuron (MNS), sensitive as well as painful (4); thalidomide, on the other hand, causes neuropathy, that is, it causes suffering of the sensory axon rather than of the body mobile phone; vincristine, paclitaxel, suramin are at the basis of sensory and motor neuropathies associated or not with autonomic impairment; still vincristine and Ara-C can also determine pure motor forms. Autonomic disorders such as constipation, orthostatic hypotension, urination disturbances are sometimes associated with sensory disturbances (1). In general, the peripheral nervous system has a great capacity for regeneration; its recovery presupposes the saving of the cell body and is often partial, even when the tumor has been successfully treated.

Chemotherapy neurotoxic syndromes are often not as specific as their diagnosis is substantially clinical-anamnestic and based on the exclusion of other possible causes of disease such as:

- Progression of the underlying disease;
- Appearance of metastases;
- Appearance of paraneoplastic syndromes;
- Appearance of other neurological complications
- Appearance of infections;
- Appearance of drug toxicity associated with antineoplastics (steroids);
- Side effects from radiation;
- Overlap of other diseases (renal, hepatic insufficiency, diabetes, hypertension).

In the diagnostic process it is first necessary to exclude the presence of brain metastases, generally responsible for focal deficits, ataxia, visual impairment, dizziness, epileptic seizures. The CT scan with contrast medium may be sufficient to highlight focal lesions, usually subcortical, located in the regions of greatest blood supply. If the patient also presents alterations in the state of consciousness or some signs of meningeal irritation it becomes necessary to exclude the hypothesis of a carcinomatosis, more frequently described in breast, lung and lymphoma tumors, or of a dissemination along the CSF pathways in tumors. primitives of the CNS. MRI is essential because it is capable of show a thickening of the dura mater or a pathological leptomeningeal and ependymal enhancement. In severe cases, neuroradiological examinations can demonstrate blockage of the CSF pathways with focal dilation of the subarachnoid spaces and ventricular system.

CHEMOTHERAPY DRUGS MOST FREQUENTLY ASSOCIATED WITH NEUROTOXICITY

The compounds most often associated with neurotoxicity phenomena and the related cell damage mechanisms will now be described in detail (10).

ANTIMETABOLITES

METHOTREXATE: It is an old drug approved both for use in oncology (in solid tumors, such as breast cancer, head-neck, gynecological but also blood cancers such as non-Hodgkin's lymphomas and lymphatic leukemia) and as a powerful first-line immunosuppressant. for rheumatic diseases (rheumatoid arthritis) and psoriasis. It is also used off-label always as an immunosuppressant in inflammatory diseases not responsive to other agents such as multiple sclerosis and systemic connective tissue diseases. In Italy, it is mainly used in the form of a solution for injection but is also available in oral tablets. All patients should be screened for tuberculosis and hepatitis B before treatment as there is a risk of reactivation. moreover, MTX interacts with many commonly used drugs, primarily non-steroidal analgesics (which can increase blood

concentrations of MTX, enhancing its toxicity) and proton pump inhibitors. Regarding the potential neurotoxicity, various forms have been described, both acute and delayed after intrathecal or endo-venous administration at high doses. The acute forms mainly concern cases of aseptic meningitis, which begins about 2-4 hours after the intrathecal injection of the compound and lasts for 12-72 hours, as well as "stroke-like" syndrome, which affects 3-10% of adults and children treated weekly with high doses of methotrexate iv. For the reduction of side effects, co-administration of calcium folinate is used, especially at high doses of methotrexate. Through this oral antidote, in fact, it is possible to tolerate higher doses of the drug without developing severe mucosal toxicity, obtaining better control of tumor forms. Calcium levofolinate is available parenterally to manage severe acute symptoms of intoxication or orally for preventive purposes. Studies on neurotoxicity are limited with respect to the effects on bone marrow and mucous membranes but it seems to have a certain preventive role. Symptoms are ictal-like with focal neurological deficits; the onset occurs on average one week after administration. Usually, the symptoms are transient and resolve spontaneously in 48-72 hours. MRI performed in the acute phase shows selective damage of the deep white matter and the corpus callosum. These alterations are detected initially only with the sequences in diffusion that demonstrate an altered diffusivity of water molecules in the tissues due to swelling and cytotoxic edema of the oligodendrocytes. Very often the clinical-radiological picture is reversible.

FLUOROURACIL: It is a pyrimidine analog antimetabolite that interferes with DNA synthesis. When used in high doses, fluorouracil can cause cerebellar syndromes. Only in rare cases can it cause optic neuropathy, oculomotor disorders, or peripheral neuropathy. It is mainly used in cases of slowly growing solid tumors like : colorectal, breast, gastric and pancreatic cancer and is also used off label for other solid tumors like cervical and endometrial or head and neck carcinoma. About possible mechanisms of resistance, resistance to the cytotoxic effects of 5-fluorouracil can be due to loss or decreased activity of enzymes required for its activation (it needs to be phosphorylated to be converted into the active molecule). So if enzymes involved in its activation are lacking or are ineffective this could represent a possible mechanism of resistance to 5-fluorouracil. It is often used in combination with other drugs, in particular in its inhibition of thymidylate synthetase an important role is played by a folate cofactor, that is 5,10-methylenetetrahydrofolate, a specific reduction product of folic acid used by cofactor and by thymidylate synthetase.

CYTOSINE ARABINOSIDE (ARA-C): The name " cytosine arabinoside" derives from the chemical composition of the molecule that combines a nitrogenous base (cytosine) with a sugar (arabinose). Cytosine normally binds to a different sugar, deoxyribose, to form deoxycytidine, a chemical component of the DNA molecule. Cytosine arabinoside is chemically similar enough to human cytosine deoxyribose (deoxycytidine) to be incorporated into human DNA. However, this alters DNA transcription and leads to cell death. It is marketed as a powder for solution for injection for intravenous use (as the drug is not active orally; Continuous intravenous infusion allows for relatively constant and effective plasma levels.) indicated primarily to induce remission in acute myeloid leukemia in adults and children and secondly in treatment of other lymphoproliferative forms.

VINCA ALKALOIDS: Vinca alkaloids are derivatives of the Vinca Rosea plant and exert their cytotoxic effect by binding to tubulin. Tubulin is found in the cell cytoplasm; the polymerized form constitutes the microtubular apparatus that gives rise to the spindle, along which chromosomes migrate during mitosis. This group of pharmacies the polymerization of the tubules and this inhibits the assembly of microtubules with the dissolution of the mitotic spindle. The cell consequently stops in metaphase during mitosis. These agents can block tumor cells during mitosis. Even if they act on the same target of Taxanes, their mechanism of action is different. Also in this case they bind to the beta-tubulin subunit of microtubules and block its ability to polymerize with the alpha subunit. They inhibit the interaction between beta-tubulin and alpha-tubulin, so the formation of the alpha beta-tubulin dimers and then the polymerization of alpha beta-tubulin dimers into the protofilaments of microtubules. So we have the opposite condition concerning the mechanism of action of taxanes. In this case, the mitotic spindle cannot form and mitosis is arrested in metaphase of the cell cycle, so in the phase in which mitotic spindle is required to allow the chromosomes to line up at the equator. So in this case we have not microtubule polymerization and mitotic spindle formation, so the cell cycle is arrested in metaphase (8).

Vinblastine is the first member of the class of Vinca Alkaloids: it is a dust to be reconstituted to be administered intravenously, the dose of which is calculated based on body weight. It's approved for the treatment of testicular cancer Kaposi's sarcoma, neuroblastoma, Hodgkin's lymphoma, leukemia, breast cancer, and lung cancer.(9) For the most commons side effects we have leukopenia and neutropenia. General Dosing Ranges in the peripheral neuropathy is 3-18 mg/ m^2/ day IV q7-10 days. Also in this case the major toxic effect, after even a single dose of Vinblastine, is represented by myelosuppression which reaches a maximum after 7-10 days of the single-dose administration. That's because they act on all rapidly dividing cells, they cannot exert a selective action on just tumor cells. The same reason is on the basis of their GI effects, in this case, their target rapidly dividing cells in the intestinal epithelium. So this is the reason for their common toxic effects. Another drug of these class Is vincristine, marketed as a solution for injection that's used for the treatment of leukemias and lymphomas in adult and pediatric patients, for non-Hodgkin's lymphoma, neuroblastoma, rhabdomyosarcoma, breast, colorectal and lung cancer and also in idiopathic thrombocytopenic purpura refractory to splenectomy and short-term steroid therapy. This one is better tolerated in children than in adults because these lasts may experience severe neurotoxicity, while it seems to have a slightly myelosuppression activity compared to Vinblastine. Side effect it could be numbness/ tingling of extremities, myelosuppression and hyponatremia etc. The reason of neurotoxicity in this case is referred to the fact that microtubules are found in high concentration in the brain, where they play an important role in the axonal transport. The severity of symptoms is related to the total dosage and duration of treatment. In 50% of patients, neuropathy presents with distal paraesthesia and muscle cramps. Below, hypoesthesia and weakness of the distal muscles of the limbs are highlighted with a deficit of extension of the carpus, fingers, feet with stepping gait.

NEUROPROTECTION STRATEGIES: FOCUS ON MICRO AND NANOPARTICLE SYSTEMS AND ORAL SUPPLEMENTATION WITH VITAMINS

The advances in the nanotechnology sector have led to the development of innovative therapeutic systems that allow optimizing the performance of drugs by minimizing some of their systemic side effects. In fact, through the physical or chemical combination of biomaterials with particular characteristics, it has been possible to create more or less sophisticated colloidal systems such as soluble polymeric systems, liposomes, micelles and lipidic, polymeric, and inorganic nanoparticles that allow acting as carriers (carriers) for numerous molecules (cargo), improving their biopharmaceutical profile[30]. The use of such systems has brought several positive aspects including:

- improving the delivery of the drug to the site of action
- the reduction of the exposure of healthy tissues to the molecules with reduction of side effects
- the improvement of the stability and absorption of excessively lipophilic or poorly absorbable compounds by biological membranes
- the exploitation of some anatomical-pathological features for therapeutic purposes (in the oncology field, for example, tumor tissues are characterized by high but incomplete vascularization, with poor lymphatic drainage, and for this reason, they are subject to passive direction systems known as the EPR effect (enhanced permeation and retention))

Using micro and above all nanoparticulate systems (nanocapsules and nanospheres) it has been possible to create pharmaceutical forms with controlled release, site-specific, useful for directing the active principle, and widely exploited in the oncology field [31].

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Using micro and above all nanoparticulate systems (nanocapsules and nanospheres) it has been possible to create pharmaceutical forms with controlled release, site-specific, useful for directing the active principle, and widely exploited in the oncology field [31]. These systems can be distinguished according to various criteria such as structural (microcapsules, or reservors, or microspheres, or matrices), historical (first, second or third generation vectors), or according to the direction mechanism (active or passive). Another very useful classification system is based on the type of material of these systems, thus recognizing inorganic particles (e.g. quantum dots, carbon nanoparticles, ceramic), nanobubbles, synthetic systems (dendrimers, micelles, polymersomes, polymer-drugs conjugates), and bio-inspired (nanogels, capsids of viral vectors, lipid systems such as liposomes and solid lipid nanoparticles)[30]. The purpose of this article is not to systematically treat all these systems as it would not be possible to synthesize all the structural and biological and applicative characteristics in such a short time but we want to dwell on their usefulness in reducing the potential neurotoxic effects of some chemotherapy molecules [31]. They can carry hydrophobic but also hydrophilic drugs in their core, they are immunologically safe as phospholipids are components of biological membranes and their surface can be modified with PEG to create targeted or invisible liposomes to the reticulo-endothelial system. Furthermore, pegylation increases their half-life and protects them from interaction with opsonizing proteins. [32]. Protein nanoparticles, on the other hand, are aggregated structures following the folding of proteins; they can act as carriers for both hydrophilic and hydrophobic drugs through covalent and non-covalent bonds and the surface can be modified with PEG or mAb. The most used proteins for this purpose are albumin, silk fibroin (this is also used to carry oligonucleotides), gelatin and elastin. In addition to the use of systems to deliver the drug to target tissues by reducing the exposure of healthy tissues and therefore the side effects, another useful neuroprotection strategy is oral supplementation with lipophilic substances such as vitamin E (tocopherols), A (retinol and derivatives) and long-chain fatty acids. Many studies done in this regard[33,34,35] show an improvement in neuropathies associated with clinically evaluated chemotherapy treatments and, at times, with neurophysiological examinations, even if such studies can hardly be generalizable given the small number of patients evaluated and the results are not always uniform, but it seems that the use of nutraceuticals improves myelination and neuronal trophism in these patients, considerably reducing symptoms and allowing non-abandonment of existing therapies.

The motor damage is often more evident than the sensory one, but the sensory deficit, unlike the motor one, tends to persist. Neuropathy is axonal; the compromise of the cranial nerves, including the optic, is rare and tends to be bilateral. One third of patients have autonomic suffering with constipation, sphincter disorders, orthostatic hypotension. Vincristine also does not cross the blood brain barrier easily. The CNS damage would be caused by the accumulation of the drug in the vascular endothelium with consequent alteration of vasoregulation, vasoconstriction up to hypoxic and ischemic phenomena prevalent in the posterior circulation(5). Vinca alkaloids, 5-fluorouracil, cisplatin, oxaliplatin and methotrexate are involved in central or peripheral forms of neurotoxicity. The first manifestations of neurotoxicity (after 4-5 weeks) particularly in patients treated with vincristine are paresthesias in the hands and feet and forms of areflexia, which are reversible and appear in the first weeks after treatment. Vincristine frequently causes constipation and more rarely intestinal obstruction due to involvement of the autonomic nervous system. Due to the involvement of the cranial nerves, ptosis of the eyelid and diplopia (2n) can occur.(23)(24) Generally the picture is reversible, but cases of laminar necrosis and permanent deficits have been described.

PLATINUM COORDINATION COMPLEXES: CISPLATIN, CARBOPLATIN, OXALIPLATIN: They are one of the most chemotherapy drug class used ones in Europe and their mechanism of action include, for cisplatin, binding with DNA, interacting with nitrogen in position 7 of two adjacent guanidine groups, forming intra and interchain adducts, causing distortion of the chromosomal segment concerned, preventing DNA transcription and replication and generating cellular apoptosis. As for Oxaliplatin, Carboplatin, they act with a mechanism similar to that of alkylating agents. (11) In the case of cisplatin (simplest one with a platinum atom two chloride atoms and two amino groups) both chlorine ions undergo a slow process of substitution by the water and thus a positively charged hydrated compound is generated. Carboplatin is the second generation developed from cisplatin to reduce toxicity(it is an analogue of cisplatin where the chlorine tomes are replaced by two organic ligands and the cytotoxic activity is 65-75 times lower in vivo, although it has a spectrum of activity similar to the previous one) and Oxaliplatin is the 3rd generation with a different resistance mechanism. Oxaliplatin is highly reactive with shorter half-life. Also effective with tumors with functional deficit of mismatch repair.

Neurotoxicity reversible peripheral neuropathy, cumulative, similar to CISPLATIN, dose- limiting. NEPHROTOXICITY is lower than CISPLATIN. The mechanism of action is the same: DNA damage. (12)(13). Cisplatin and oxaliplatin, on the other hand, are frequently involved in peripheral neuropathies (polyneuritis) with paraesthesia / dysaesthesia, tremors / spasms, etc. The duration of symptoms increases with the number of cycles although it is usually reversible, although cumulated doses can give rise to irreversible disorders **(**25**)**. Neurotoxicity is reversible with peripheral neuropathy limb paraesthesia, tremors , visual disturbances; is a common side effect of platinum-based chemotherapy that may cause dose reduction and discontinuation, with oxaliplatin being more neurotoxic(14).

BLEOMYCIN: It is an alkylating- agent, a natural antibiotic produced by streptomyces verticillus. It binds iron in the presence of oxygen and transfers an electron. There is a transfer of electrons from Fe2+ to molecular oxygen.
It becomes a reactive species with ROS formation (free radical, oxidative damage). Its main damage is the introduction of SSB and DSB in DNA like that caused by ionizing radiation. SSB becomes DSB when they meet the replication fork. Cells accumulate in G2. As regard toxicity we have cutaneous most frequent one (hyperpigmentation, erythema, ulceration), Pulmonary most serious one and myelosuppression less than other alkylating-agents (15).

TAXANES: It is clear that this drug is able to promote and stabilize microtubule assembly and prevent microtubules depolimerysation /disassembly. These drugs are also referred as "microtubules stabilizers". (16) The reason of their effectiveness as antimicotic agents (and thus as anticancer drugs) is due to their compounds, which stabilize microtubules and prevents depolymerization, so the cell becomes so clogged with microtubules that it cannot continue to divide. Then there is the inhibition of the progression from metaphase to anaphase because it requires mitotic spindle depolymerization.(17)(18) Only if mitotic spindle depolymerized, so only if microtubules disassemble, sister chromatids movement to the opposite poles is possible.(19) Common adverse effects can be hypersensitivity , athralgia / myalgia, peripheral neuropathy, opportunistic infections and radycardia. In recent years, a new formulation of Paclitaxel has been produced, which is the NAB PACLITAXEL, such as albumin-bound nanoparticle solution of paclitaxel, in order to improve its delivery and its pharmacodynamic properties. Taxanes are highly hydrophobic and albumin is a natural carrier for lipophilic molecules. Paclitaxel is the new formulation of albumin-bound paclitaxel in nanoparticle formulation can bind to gp60, the albumin receptor on endothelial cells, which in turn activates caveolin-1 and the formation of caveolae. The formation of caveolae is the process through which the albumin-paclitaxel complex can be released outside the blood circulation through a process of exocytosis. Neurotoxicity, manifested primarily by a motor and sensory polyneuropathy, is the principal nonhematological side effect of Taxanes(20). (21).

IMMUNOTHERAPY AND MONOCLONAL ANTIBODIES DRUGS: GENERAL ASPECTS AND NEUROTOXICITY: Immunotherapy represent a new pillar in cancer treatment because malignant neoplasms have the ability to evade the immune system, proliferate and metastasize; so the goal of immunotherapy is to exploit specificity and memory a long-term adaptive immune response to achieve lasting tumor regression and possible cure, although to date this has only been achieved in a small subset of patients. Numerous inhibitory signaling pathways of immune systems are used for maintaining self-tolerance and homeostasis: the molecules involved in these pathways are collectively referred to as immune checkpoints. The primary role of immune checkpoints is to protect the tissues from damage when the immune system responds to pathogens and maintain tolerance to self-antigens. This is mainly achieved by adjusting the activation or effector function of T cells (2). The first checkpoint receptor that was successfully studied and tested as an immunotherapy target is CTLA-4. It is expressed on activated T cells and its primary function is to downregulate the extension of the activation of T lymphocytes by counteracting the co-stimulatory signal delivered by CD28. Ipilimumab, an anti-CTLA-4 monoclonal antibody, was the first inhibitor of an immune checkpoint to receive FDA approval for the treatment of advanced melanoma. It binds to CTLA-4 and blocks its immunosuppressive signal.
As a result, activated T cells, including those activated by tumor antigens, can continue to proliferate, produce cytokines and perform their effector functions cytotoxic in the tumor microenvironment. Another immune checkpoint receptor, the programmed death receptor 1 (PD1) and its ligands, the programmed cell death ligand 1 (PD-L1) and the programmed cell death ligand 2 (PD-L2). Similarly to CTLA-4, PD-1 plays a key role in regulating and maintaining the balance between T cell activation and immune tolerance(26). Unlike CTLA-4, however, PD-1 is widely expressed and can be found not only on the surface of T cells but also on that of B and NK cells. The PD-L1 ligand is commonly upregulated on several human solid tumors, including melanoma, lung and ovarian cancers. Several anti-PD1 / anti-PDL1 drugs, including atezolizumab, pembrolizumab, nivolumab, and durvalumab, are in various stages of clinical development and / or approved for certain cancer types. Pembrolizumab and nivolumab have shown good success in the treatment of several types of cancers, including melanoma, small cell lung, renal cancer and their use is also promising for other cancers under study. Nivolumab is approved for metastatic melanoma, metastatic NSCLC, advanced renal carcinoma, refractory Hodgkin lymphoma (ORR 87%); pembrolizumab is approved for metastatic melanoma (ORR 26%), metastatic NSCLC expressing PD-L1, refractory Hodgkin lymphoma, metastatic urothelial tumors (22).

Atezolimumab is used in metastatic resistant NSCLC and locally in advanced or metastatic urothelial carcinoma. For the toxicity we have fatigue, dyspnoea, nausea, cough, costopation, musculoskeletal pain, immune-related effects (hepatitis, colitis, hypophysitis, diabetes, pancreatitis, thyroid disorders, adrenal insufficien- cy). Durvalumab (from 2017) is used in metastatic urothelial cancer and avelumab is used also in Merkel cell cancer. All this have antibodies against PD-L1. Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4), Programmed Death 1 (PD-1) / Programmed Death Ligand-1 (PD-L1) checkpoint inhibitors have been shown to have a relevant clinical value in a large number of solid tumors, leading to an improvement of progression free survival and overall survival in comparison to standard chemotherapy (27). Safety analysis showed that immunotherapy is well-tolerated and the most common side effects are usually manageable (28). Moreover, several trials reports a better quality of life in patients treated with immunotherapy compared to patients treated with standard chemotherapy. Adverse events related to

immunotherapy treatment are toxicities caused by non-specific activation of the immune system and can affect all organs. Among them we remember dystyroidism, nephritis, skin rash, myalgia, pneumonia, gastroenteritis and ocular inflammation. Monoclonal antibodies are a class of high molecular weight drugs specific for only one antigen which are produced with the recombinant DNA technique. The first mAbs entered the market in the early 2000s and currently make up about 30% of approved drugs and over 50% of those under study. They are in fact immunoglobulins (usually IgG) that are produced normally by the plasma cell; in the beginning, the first generation was produced by the hybridoma techniques using the murine model ; this technique is still used for monoclonal antibodies that are used for analysis but cannot be used for humans because humans can recognize the antibody of the mouse as a foreign molecule and eliminate it through the immune system. Moreover, antibodies produced in the murine system can recognize just antigens that they recognize as immunogenic that are not always the same we find in humans. One of the problem is the production cost: large proteins containing disulfide bonds and post-translational modifications: need for a sophisticated eukaryotic cells as bioreactors. They require glycosylation modifications (a post-translational modification); that also affects the binding with the Fc receptor. Another big problem of monoclonal antibodies is the high molecular size, together with their hydrophilicity which prevents them from being absorbed enterally, so they need to be administrated injecting. They are also immunogenic as molecules recognized as foreign by the host's immune system and this can lead to the development of anti-drug antibodies, reducing their effectiveness, or to allergy or autoimmunity phenomena against self by molecular mimicry. As regards the neurotoxicity due to monoclonal antibodies, the studies, although still quite limited, in some cases show two main problems (29):

- Dysimmune neuropathies linked to the administration of anti-PDL1 type polyoneuropathies demyelinating of the peripheral system guillain barrè-like
- Reversible posterior vascular encephalopathies following anti-VEGF administration such as bevacizumab

Even though these events are rare, they are of high relevance as the rate of residual symptoms or even fatal outcomes is remarkable. The frequency of immune checkpoint-inhibitor therapy inducing neurological adverse events is about 1% in larger studies (29).

Conflict of Interest Statement: the authors had no conflicts of interest to declare. For the purposes of compliance with the provisions of art. 6-bis of Law no. 241/1990 and of the art. 7 of the Code of Conduct for public employees, issued with Presidential Decree no. 62/2013;

- aware of the penal sanctions resulting from untruthful declarations and / or falsehoods in acts;
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REFERENCES

1. Comu. Collegio degli oncologi medici italiani. *Manuale di oncologia medica.* Edizioni minerva medica, 2018
2. Ciardiello F, *oncologia medica 2 edizione.* Idelson-gnocchi, 2017
3. Sifo, standard tecnici di galenica oncologica 2012-2016. https://www.sifoweb.it/images/pdf/pubblicazioni/altreedizioni/Galenica_Oncologica/Standard_tecnici_di_Galenica_Oncologica.pdf
4. Cammarata S, Capone G, Orlando V. La farmacovigilanza dei medicinali per uso umano il ruolo delle agenzie regolatorie. In: Novellino E. Il farmaco: ricerca, sviluppo e applicazione in terapia. FedOA editore, 2019 Erbetta A, Lauria G, Sghirlanzoni A. Complicazioni della chemioterapia. In: Sghirlanzoni A, Simonetti F, Caraceni A. le complicanze neurologiche in oncologia. Springer, 2006
5. Chi H, et al - Chemotherapy and Surgery in Colon Cancer: for Better Treatment Outcomes https://www.frontiersin.org/research-topics/14359/chemotherapy-and-surgery-in-colon-cancer-for-better-treatment-outcomes
6. Xiying F, - Efficacy of Drug Interventions for Chemotherapy-Induced Chronic Peripheral Neurotoxicity: A Network Meta-analysis
7. Fazilath U, et al - Endophytic Fungi—Alternative Sources of Cytotoxic Compounds: A Review
8. Bayssas, M J Gouveia, F De Vassal, J L Misset, L Schwarzenberg, P RIBAUD, M Musset, C Jasmin, M Hayat, G Mathé - Vindesine: a new vinca alkaloid
9. Consiglio Nazionale Delle Ricerche - Farmaci antitumorali, scoperto il ruolo del platino nella resistenza alla chemioterapia
10. Nathan P, et al - Platinum-induced peripheral neurotoxicity: From pathogenesis to treatment
11. Mcwhinney S, ET AL- Platinum neurotoxicity pharmacogenetics
12. Calls A, ET AL - Pathogenesis of platinum-induced peripheral neurotoxicity: Insights from preclinical studies
13. Ozkan K, ET AL - Platinum-induced neurotoxicity: A review of possible mechanisms
14. Hay J ET AL - Mechanisms of bleomycin-induced lung Damage
15. Da Costa R, Giselle F Passos, Nara L M Quintão, Elizabeth S Fernandes, João Raphael L C B Maia, Maria Martha Campos, João B Calixto - Taxane-induced neurotoxicity: Pathophysiology and therapeutic perspectives
16. Tamburin S, Susanna B Park, Alberti ET AL- Taxane and epothilone-induced peripheral neurotoxicity: From pathogenesis to treatment
17. Hagiwara H, Sunada H - Mechanism of taxane

neurotoxicity
18. PARK S, Goldstein D, ET AL - Chemotherapy-induced peripheral neurotoxicity: a critical analysis
19. Rowinsky, E K V Chaudhry, D R Cornblath, R C Donehower - Neurotoxicity of Taxol
20. Ciruelos M, Cantos C, Noelia Martinez-JÁÑEZ, Coralia Bueno-Muiño, et al - A Pilot, Phase II, Randomized, Open-Label Clinical Trial Comparing the Neurotoxicity of Three Dose Regimens of Nab-Paclitaxel to That of Solvent-Based Paclitaxel as the First-Line Treatment for Patients with Human Epidermal Growth Factor Receptor Type 2-Negative Metastatic Breast Cancer
21. Feng S, Coward J, Mccaffrey E, Coucher J, Kalokerinos P, KEN O'byrne - Pembrolizumab-Induced Encephalopathy: A Review of Neurological Toxicities with Immune Checkpoint Inhibitors
22. Lee Dellon, A Patrick Swier, Chris T Maloney JR, Melvin S Livengood, Scott Werter - Chemotherapy-induced neuropathy: treatment by decompression of peripheral nerves
23. Alberti P, Cavaletti G, Cornblath D, - Toxic neuropathies: Chemotherapy Induced Peripheral Neurotoxicity
24. PK PAL - Clinical and electrophysiological studies in vincristine induced neuropathy.
25. Giannatempo P, L'immunoterapia in oncologia. From: rivista società italiana di medicina generale, numero 3, 2018. https://www.pacinimedicina.it/wp-content/uploads/13_oncologia.pdf
26. Akkın, S, Varan, G., & Bilensoy, E. (2021). A Review on Cancer Immunotherapy and Applications of Nanotechnology to Chemoimmunotherapy of Different Cancers. *Molecules (Basel, Switzerland)*, *26*(11), 3382. https://doi.org/10.3390/molecules26113382
27. Lei, Q., Wang, D., Sun, K., Wang, L., & Zhang, Y. (2020). Resistance Mechanisms of Anti-PD1/PDL1 Therapy in Solid Tumors. *Frontiers in cell and developmental biology*, *8*, 672. https://doi.org/10.3389/fcell.2020.00672
28. Möhn, N., Beutel, G., Gutzmer, R., Ivanyi, P., Satzger, I., & Skripuletz, T. (2019). Neurological Immune Related Adverse Events Associated with Nivolumab, Ipilimumab, and Pembrolizumab Therapy-Review of the Literature and Future Outlook. *Journal of clinical medicine*, *8*(11), 1777. https://doi.org/10.3390/jcm8111777
29. Caliceti P. Bioconiugati per il delivery attivo di farmaci. In: la chimica e l'industria | anno xcviii n° 3 | maggio/giugno 2016. https://www.soc.chim.it/sites/default/files/chimind/pdf/2016_3_10_ca.pdf
30. Genta I, Modena T, Conti B, Dorati R. Sistemi terapeutici micro e nanoparticellari iniettabili. In: la chimica e l'industria | anno xcviii n° 3 | maggio/giugno 2016. https://www.soc.chim.it/sites/default/files/chimind/pdf/2016_3_18_ca.pdf
31. Colombo P, Conti B, Alhaique F, Vidale E. Principi di tecnologia farmaceutica seconda edizione. Casa editrice ambrosiana, 2015
32. Pace, Andrea & Galiè, Edvina & Koudriavtseva, Tatiana. (2012). Neuroprotective strategies in the prevention of chemotherapy-induced neuropathies. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 21. 10.1007/s00520-012-1552-2.
33. Eum, Seenae & Choi, Hye-Duck & Chang, Min Jung & Choi, Ho-Chun & Ko, Young-Jin & Ahn, Jeong-Soo & Shin, Wan-Gyoon & Lee, Juyeun. (2013). Protective Effects of Vitamin E on Chemotherapy-Induced Peripheral Neuropathy: A Meta-Analysis of Randomized Controlled Trials. International journal for vitamin and nutrition research. Internationale Zeitschrift für Vitamin- und Ernährungsforschung. Journal international de vitaminologie et de nutrition. 83. 101-11. 10.1024/0300-9831/a000149.
34. Stankovic, J., Selakovic, D., Mihailovic, V., & Rosic, G. (2020). Antioxidant Supplementation in the Treatment of Neurotoxicity Induced by Platinum-Based Chemotherapeutics-A Review. *International journal of molecular sciences*, *21*(20), 7753. https://doi.org/ 10.3390/ijms21207753

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