SPECIAL ARTICLE

Systemic anticancer therapy-induced peripheral and central neurotoxicity: ESMO—EONS—EANO Clinical Practice Guidelines for diagnosis, prevention, treatment and follow-up☆

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INTRODUCTION

Central and especially peripheral neurotoxicities due to systemic antineoplastic therapy are common and often dose-limiting side-effects. In patients with chemotherapy (ChT)-induced peripheral neurotoxicity (CIPN), recovery is in general partial with residual deficits in most patients. In these Clinical Practice Guidelines, recommendations on diagnosis, prevention and treatment of peripheral neurotoxicity and specific aspects of central neurotoxicity due to antineoplastic therapy are given. Recommendations regarding immune-related neurotoxicity due to immune checkpoint inhibitors are described in depth in the ESMO Clinical Practice Guidelines on 'Management of toxicities from immunotherapy'.[1]

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PERIPHERAL NEUROTOXICITY

Although the 'N' in CIPN generally stands for 'neuropathy', the well-established involvement of dorsal root ganglia neurons (and not only of peripheral nerves) after the administration of several ChT regimens suggests that the term 'peripheral neurotoxicity' is more appropriate in this specific context.

Incidence and risk factors

Incidence. According to the individual antineoplastic drug, the incidence, severity and clinical pattern of CIPN during treatment varies considerably as shown in supplementary Tables S1 and S2, available at https://doi.org/10.1016/j.annonc.2020.07.003. With regard to long-term toxicity, a study on 512 female cancer survivors showed that 47% of women suffered from CIPN (median 6 years) after treatment.[2]

Therapy-associated risk factors. CIPN occurs in a dose-dependent manner usually after several cycles of neurotoxic antineoplastic therapy and is typically dependent on the administered single and cumulative doses, although duration of exposure, scheduling and combination therapies are also potential risk factors (supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.07.003).

Individual risk factors. Individual risk factors for developing CIPN are not yet clearly established. For instance, diabetes

mellitus and increasing age (often defined as $\geq$75 years) have been proposed as strong independent risk factors.[3] However, concurrent exposure to other neurotoxic agents and pre-existing neuropathy, as well as diseases/deficiencies *per se* predisposing to neuropathy, should be considered as potential risk factors [alcohol abuse, renal insufficiency, hypothyroidism, vitamin deficiency, infections like human immunodeficiency virus (HIV) and autoimmune rheumatologic conditions] [IV, B].[4−6] Smoking seems to increase the risk of long-term prevalent paraesthesia, as reported among 1409 long-term Norwegian survivors of testicular cancer.[7]

There have been many attempts to identify genetic markers carrying a high risk of developing CIPN. However, none of the individual single nucleotide polymorphisms identified so far has sufficient prognostic value for use in clinical practice.[8] In cases with severe neurotoxicity, for instance motor involvement due to vincristine-induced CIPN, relevant predisposing neurological diseases such as axonal Charcot Marie Tooth type 1A should be ruled out. These patients usually present with predominant motor involvement and distinct deformities (hollow foot, stork legs).[9]

Assessment/diagnosis

Clinical pattern. The most common clinical presentation of CIPN is a predominant sensory axonal neuropathy with occasional motor and autonomic involvement. Predominantly sensory fibres are affected, but some cytostatic agents cause a sensory-motor pattern. Symptoms of CIPN typically occur during the first 2 months of treatment, progress during active antineoplastic treatment, and then usually stabilise soon after treatment is completed. However, drug-specific features like paclitaxel- or oxaliplatin-induced acute neurotoxicity or even 'coasting phenomenon' as worsening of neuropathic syndromes after cessation of therapy have to be considered (e.g. with platinum drugs or paclitaxel; see supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2020.07.003).

With some antineoplastic agents (e.g. platinum compounds, vinca alkaloids, taxanes and thalidomide), cell bodies in the dorsal root ganglion are more vulnerable to neurotoxic damage (often irreversible), due to less protecting blood brain barrier leading to sensory neuronopathy (ganglionopathy). The clinical picture may be asymmetrical and predominantly involves proprioception sense but does not exclude the motor system.

Large sensory nerves are most commonly affected in CIPN by toxicity in a symmetrical length-dependent manner (dying back axonopathy). Therefore, typical clinical symptoms are predominantly sensory and usually include the following neuropathic so-called 'plus' features: acral pain and paraesthesia (tingling like pins and needles), accompanied by dysaesthesia, allodynia and hyperalgesia. Sensory loss appears in a 'glove and stocking type' distribution and leads to 'minus' symptoms like numbness in hands and feet, including impaired perception of light touch, vibration sense, pin prick (hypoalgesia) and proprioception (tuning fork test) in clinical examination.

Small fibre neuropathy represents affection of nerve terminals of fibres involved in temperature and pain perception, which is, for example, present in patients treated with vinca alkaloids, taxanes, thalidomide and bortezomib. It leads to painful sensation of burning feet (and/or hands) and even lancinating pain, which can be easily potentiated by pin-prick testing. In clinical examination, decreased pain perception and temperature sensation is typical in painful areas.

Involvement of motor fibres (associated with reduction or absence of deep tendon reflexes or even distal weakness, atrophy of small feet muscles, tremor, cramps) or autonomic or cranial nerve symptoms appear much more seldom than sensory damage.

Autonomic involvement which is typical for small fibre damage with vincristine and bortezomib use can lead to abdominal pain, constipation, postural hypotension, bladder disturbances, delayed gastric emptying and reduced variability of heart rate.

Practical aspects of assessment. The early detection of CIPN is a key factor for an adequate management. A baseline and ongoing clinical evaluation (before every cycle) of physical function is a critical but often overlooked aspect.[10] A practical assessment approach for CIPN is summarised in Figure 1. A consequent ongoing assessment could enable the health care professionals to discover potential or pre-existing symptoms before the neuropathy becomes irreversible [IV, A]. Therefore, the pretreatment assessment may also require the consultation of a neurologist if uncertainness occurs.

Until now, no biomarker has proven useful for diagnosing and monitoring CIPN, although serum neurofilament light (NfL) determination, currently in development, appears to be a promising tool.[11] So far, it cannot be recommended in daily routine practice.

Neurophysiological examination. Conventional neurophysiological methods [electromyography (EMG) with nerve conduction studies] may provide complementary information to clinical assessment and may identify pre-existing, sometimes still subclinical, neuropathy, as separate risk factors for CIPN. Axonal degeneration is evident as progressive reduction of sensory nerve action potential (NAP) amplitude [if motor fibres affected: compound muscle action potential (CMAP) correlating with axonal damage in EMG] followed by impairment of nerve conduction velocity. However, conventional nerve conduction parameters often do not mirror the patients' symptoms and are not suitable to monitor severity of CIPN during therapy. Furthermore, it is often noted that despite improvement in patients' symptomatic clinical and functional recovery, neurophysiologic assessment shows only a modest improvement. Additional assessment tools like somatosensory potentials may clarify if proximal sensitive nerves have been affected or the presence of comorbidities in rare cases. An EMG may demonstrate
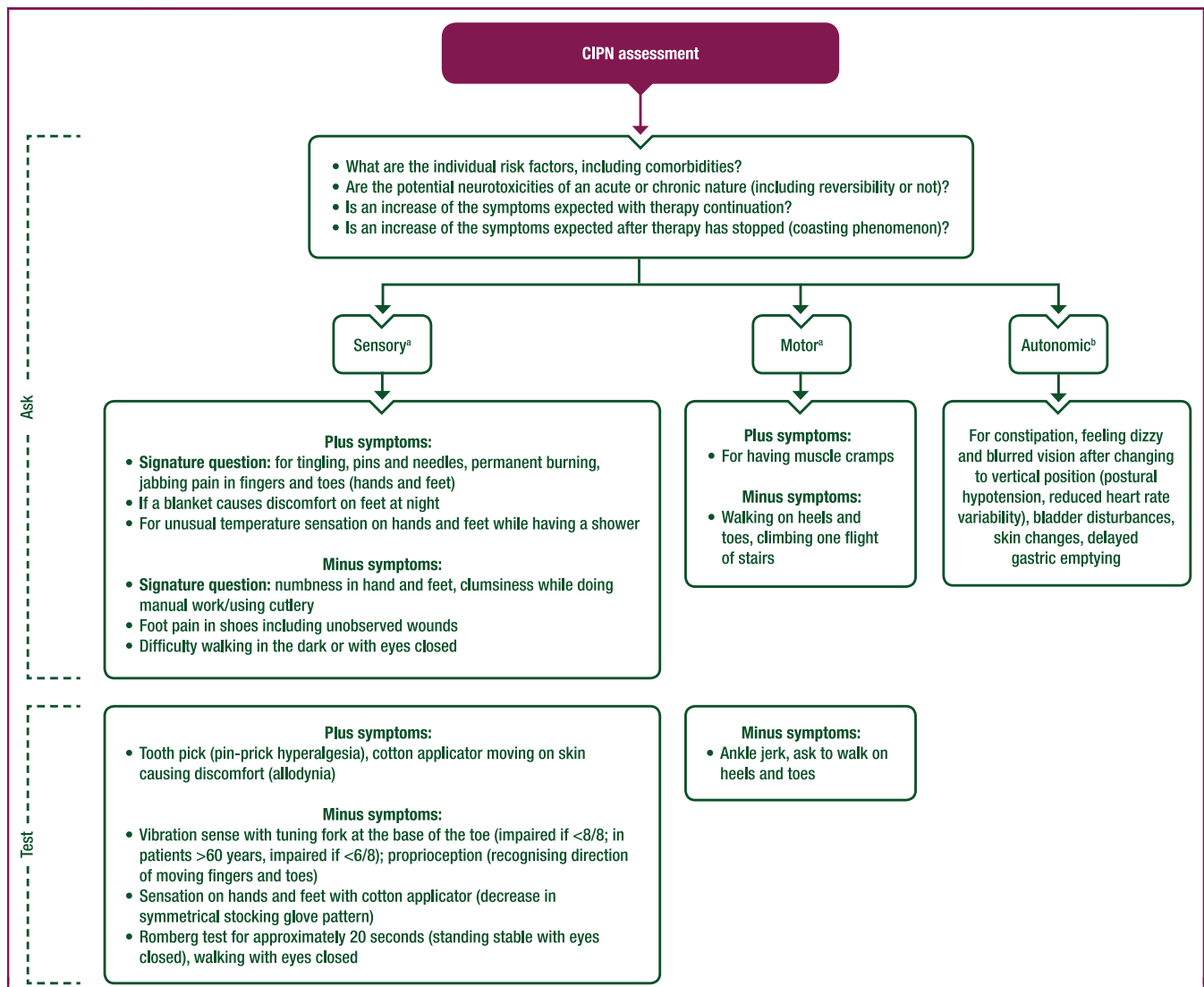
Figure 1. Practical approach for CIPN assessment.
CIPN, chemotherapy-induced peripheral neuropathy.
[a] Consider neurophysiology in case of asymmetric pattern of symptoms and/or normal clinical examinations despite patients' complaints. However, be aware of normal neurophysiology in case of small fibre neuropathy.
[b] If autonomic neuropathy is suspected, neurophysiology including sympathetic skin response and heart rate variability should be conducted.

acute hyperexcitability and chronic neurogenic changes due to motor axonopathy but is not needed for clinical routine. In small fibre neuropathies (e.g. bortezomib), all findings based on standard neurophysiological techniques may be normal and only skin biopsy examined by an experienced pathologist (gold standard) may demonstrate degeneration of small C (heat) and Aδ (cold) fibres.

Assessment tools—CIPN outcome measurements. In general, health care professionals tend to underestimate symptoms experienced by patients and that patients' perception of CIPN is different from that of their health care professionals.[12-14] Some specific clinician-reported outcome measurements (CROMs) and patient-reported outcomes measures (PROMs) examples are given in supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2020.07.003. None can be formally recommended over the others.

Prevention of CIPN

Recommendations for or against the use of pharmacological and non-pharmacological prevention strategies for CIPN are listed in Table 1.

Pharmacological prevention. Many pharmacological agents have been studied for their potential to prevent neuropathy. Until now, no effective agent exists to prevent CIPN and, therefore, no positive recommendation can be given for any of the studied agents as shown in Table 1.

Non-pharmacological prevention. The available evidence discourages the use of acupuncture to prevent CIPN. The usefulness of cryotherapy is very often discussed and, therefore, more details are given. Cryotherapy with frozen socks or gloves showed some promising results in small studies.[15,16] In the largest randomised phase III study (*n* = 180) to-date, no difference in CIPN subscales using the

Table 1. CIPN prevention: studied interventions

Intervention	Comments	LoE/GoR	References
Pharmacological intervention (none of these can be recommended)			
ALC	ALC therapy resulted in significantly worse CIPN over 2 years	I, E	[71]
Acetylcysteine	Oxaliplatin-based ChT	II, D	[72]
Alpha-lipoic acid	Platinum-based ChT	II, D	[73]
Amifostine	Platinum- and taxane-based ChT	I, D	[74]
Amitriptyline	Vinca alkaloids, platinum-based or taxanes	II, E	[75]
Calcium/magnesium	Exclusively oxaliplatin-based ChT	I, E	[76]
Calmangafodipir[a]	So far only positive randomised phase II study, phase III study (POLAR programme) is ongoing	No recommendation possible	[77]
Carbamazepine	Oxaliplatin-based ChT	II, E	[78]
DDTC	Cisplatin-based ChT	I, E	[74,79]
GSH	Platinum- and taxane-based ChT	I, E	[74,80]
Goshajinkigan	Platinum- and taxane-based ChT	I, D	[81]
Minocycline	Taxane-based ChT	II, D	[82]
MR309, selective sigma-1 receptor antagonist	So far only a positive randomised phase II study (potential neuroprotective)	No recommendation possible	[83]
Nimodipine	Cisplatin-based ChT	II, E	[72]
Omega-3 fatty acids	Taxane-based, positive outcome but small sample size ($n = 57$), not enough evidence to support the use	II, D	[84]
Vitamin B	Taxane-, oxaliplatin- or vincristine-based ChT	II, D	[85]
Vitamin E	Platinum- and taxane-based ChT	II, D	[74]
Multivitamin use	DELCaP study. Patients were asked for multivitamin use. Those who used multivitamins had a reduced risk of CIPN, but this was probably a surrogate for other related behaviours, which might be the actual drivers of the association with reduced CIPN	III, D	[86]
Non-pharmacological intervention			
Acupuncture	($n = 48$), outcome of electroacupuncture was worse than with sham acupuncture	II, E	[87]
Exercise	Many early reports suggest a possible protective effect of exercise on CIPN	II, C	[20]
Compression therapy using surgical gloves	In one study, additional drugs such as duloxetine were allowed	III, C	[18,19]
Cryotherapy with, for example, frozen socks and gloves	Most evidence available for taxane therapy	II, C	[15—17,88]

ALC, acetyl-L-carnitine; ChT, chemotherapy; CIPN, chemotherapy-induced peripheral neuropathy; DDTC, diethyldithiocarbamate; GoR, grade of recommendation; GSH, glutathione; LoE, level of evidence.
[a] Antioxidant agent, mimicking the mitochondrial enzyme manganese superoxide dismutase, thereby protecting cells from oxidative stress.

European Organisation for Research and Treatment of Cancer ChT-induced peripheral neuropathy 20-item scale (EORTC QLQ CIPN 20) was reported between intervention arms (frozen gloves on both hands versus no frozen gloves) with a considerably high rate of discontinuation due to discomfort.[17] However, some neuropathy symptoms were reduced. Although the study results are somewhat heterogeneous, the prevention of CIPN with cryotherapy can be considered [II, C].

There is less evidence for the efficacy of compression therapy using surgical gloves. In a small study with 42 patients receiving albumin-bound (nab)-paclitaxel, patients act as their own control wearing surgical gloves on one hand and leaving the other hand ungloved.[18] Less neuropathy [subjective measurement by Common Terminology Criteria for Adverse Events (CTCAE) and peripheral neuropathy questionnaire (PNQ)] was seen in the gloved hand compared with the other (ungloved) hand. Of note, the incidence of CIPN was only measured during four cycles of nab-paclitaxel. In another study ($n = 43$), no difference in the incidence of nab-paclitaxel-induced CIPN using either cryotherapy or compression therapy could be found.[19] As

there seems to be little harm with this intervention, it can be considered as a preventive measure [III, C].

Many early reports suggest a possible protective effect of exercise and functional training on CIPN. Therefore, medical exercise [e.g. Exercise for Cancer Patients (EXCAP©®)] to improve muscular strength and sensorimotor functions (distal motor skills, body coordination and balance) can be offered to patients at risk of developing CIPN [II, C].[20] In addition, self-management exercise interventions should be incorporated into the protocol. Contraindications must be ruled out before starting any medical exercise.[4]

Treatment of CIPN

Pharmacological treatment. Efficacious pharmacological therapeutic options for patients with established CIPN are limited. When patients experience chronic CIPN, treatment approaches focus on reduction or relief of neuropathic pain [IV, A]. Of note, the treating physician should always be aware that neuropathic pain may be aggravated by sleep disturbance, anxiety, depression and central sensitisation of pain. In order to decrease the probability of central pain

Table 2. CIPN therapy: pharmacological interventions

Intervention	Comments	Dosing used in referenced study	LoE/GoR	References
Oral drugs				
SSRIs				
Duloxetine	Reduction of neuropathic pain: cisplatin-treated patients better than taxane-treated patients	30 mg/day for 1 week, then 60 mg/day	I, B	[22,89]
Venlafaxine	Small randomised trial (n = 48), reduction of acute and chronic neuropathic pain in oxaliplatin-treated patients	50 mg initially, followed by 37.5 mg twice/day	II, C	[23]
Anticonvulsants				
Gabapentin	Trial in CIPN was negative. Established efficacy for other forms of neuropathic pain; other dosing in non-CIPN studies: 1200—3600 mg/day	Targeted dose: 2700 mg/day	II, D	[90]
Pregabalin	Trial in PN due to cancer. Established efficacy for other forms of neuropathic pain	Targeted dose: 300 mg twice/day	II, C[a]	[91]
Lamotrigine	No difference to placebo, higher dropout rate in the lamotrigine arm	Starting dose: 25 mg/day; Targeted dose: 300 mg/day	II, E	[92]
Tricyclic antidepressants				
Amitriptyline	Small randomised trial (n = 44), small improvement of CIPN, trend for improvement of QoL	Starting dose: 10 or 25 mg/day; Targeted dose: 50 mg/day	II, C	[93]
Nortriptyline	Small randomised trial (n = 51) cisplatin ChT, no significant differences between arms	Target maximum dose: 100 mg/day	II, D	[94]
Opioids				
Tramadol	Established efficacy for other forms of neuropathic pain, also a serotonin-noradrenaline reuptake inhibitor, NNT: 4.7	Tramadol 200—400 mg in two (extended release) or three doses	II, C[a]	[24]
Strong opioids	Established efficacy for other forms of neuropathic pain, salvage option, NNT: 4.3	Smallest effective dose	II, C[a]	[24]
Other				
Glutamine	Modest evidence for efficacy in children; so far, no recommendation is possible in adults			[95]
Topical local intervention				
Topical low-concentration menthol cream	(n = 51), improvement in pain scores (BPI) after 4—6 weeks	1% menthol creme twice/day to affected area and corresponding dermatomal region of spine	III, B	[27]
Topical baclofen, amitriptyline, ketamine gel	Effect after 4 weeks on CIPN 20, especially on motor subscale	10 mg baclofen, 40 mg amitriptyline and 20 mg ketamine	II, C	[28]
Topical ketamine and amitriptyline	(n = 462), no benefit was observed	2% ketamine, 4% amitriptyline	I, D	[29]
Capsaicin-containing patches, 8%	Most established efficacy for other forms of neuropathic pain, one small study in CIPN (n = 16)	Assisted capsaicin application 30 min on affected regions for 60 min, effect lasting 90 days	I, C[a] and III, C for CIPN	[30,31]

BPI, Brief Pain Inventory; ChT, chemotherapy; CIPN, chemotherapy-induced peripheral neuropathy; GoR, grade of recommendation; LoE, level of evidence; NNT, number needed to treat; PN, polyneuropathy; QoL, quality of life; SSRI, selective serotonin reuptake inhibitor.
[a] Evidence from studies in neuropathic pain other than CIPN.

sensitisation, early pain management is of utmost importance.[21]

Recommendations for or against the use of pharmacological treatment strategies for CIPN are listed in Table 2.

Oral drugs.

Selective serotonin reuptake inhibitor. Duloxetine is so far the only studied drug in CIPN in a large randomised trial showing a moderate clinical benefit in patients with painful CIPN. In 231 patients with CIPN, a higher rate of pain reduction was found with duloxetine versus placebo (59% versus 38%).[22] The effect of duloxetine treatment has been shown to be more pronounced in CIPN, due to platinum-based therapies, than in taxanes. Thus, duloxetine is recommended for the treatment of neuropathic pain [I, B] (Table 2). Venlafaxine has also been shown to be effective in a small randomised trial (n = 48) and can be considered for the treatment of neuropathic pain [II, C].[23]

Anticonvulsants and tricyclic antidepressants. Anticonvulsants and tricyclic antidepressants have shown lesser proven efficacy (Table 2). Based on the knowledge in treating neuropathic 'plus' symptoms in general, membrane stabilising agents such as anticonvulsants (pregabalin, gabapentin) or tricyclic antidepressants may have the potential for symptom control in patients with CIPN. This might be a reasonable option if duloxetine has failed or contraindications are present. From the practical side, it is important to apply all of these suggested agents against neuropathic pain at least for 2 weeks at the appropriate dose in order to assess their efficacy before changing to another option [V, B].

Opioids. As a salvage option, opioids may be used to relieve neuropathic pain, but evidence is available for neuropathic pain from causes other than antineoplastic therapies (Table 2).[24,25] There are no compelling data to

suggest that one opioid is better than another one for neuropathic pain.

Miscellaneous. There are no data supporting the benefit of nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids in the setting of CIPN. However, an anti-inflammatory effect on nociceptor involvement in temperature fibre pain has been experienced and pathological evidence of the effect of immune-modulation has been provided in an animal model of CIPN induced by bortezomib.[26]

Topical local intervention. Studied topical interventions are shown in Table 2. Based on the pathogenic mechanism of neurotoxicity, they should be primarily used in clinical suspicion of small fibre neuropathy.

Menthol. In a phase II trial, 1% menthol cream was applied to the affected area and 31 of 38 assessable patients showed substantial pain relief with minimal toxicity ($P < 0.001$).[27] Although data from randomised studies are unavailable, topical low-concentration menthol cream should be considered as the cost is low and no adverse events have been reported [III, B].

Topical baclofen/amitriptyline/ketamine. Topical treatment with a baclofen/amitriptyline and ketamine-containing gel showed a non-significant improvement in sensory neuropathy in a randomised trial ($n = 208$).[28] Significant improvement was noted in secondary outcome parameters such as the motor subscale. Its use might be considered [II, C]. In contrast, a topical amitriptyline/ketamine preparation was studied in 462 patients in a randomised, controlled trial (RCT) showing that CIPN pain, numbness or tingling could not be alleviated.[29] Its use is not recommended [I, D].

Capsaicin 8%-containing patches. Most of the available evidence for capsaicin 8%-containing patches derives from non-CIPN studies (mostly in patients with diabetes mellitus).[30] A few attempts were also carried out in patients with

painful CIPN.[25,31] Capsaicin 8%-containing patches can be considered in patients with CIPN [III, C].

Non-pharmacological treatment. In addition, or if pharmacologic therapy fails, use of certain non-pharmacological strategies may be offered to the patient with CIPN. Recommendations for or against the use of non-pharmacological treatment strategies of CIPN indicated by the grade of recommendation are listed in Table 3.

Physical exercise. Many physical exercise approaches lack strong scientific evidence due to the fact that physical exercise normally has been applied in a multimodal setting.[32] However, the evidence is growing that physical exercise and functional training (e.g. vibration training) reduces CIPN symptoms.[20,33,34] Training to improve coordination, sensorimotor and fine motor function should begin (at the latest) with the onset of manifest CIPN, but can be started earlier, at the time when potentially neurotoxic cancer treatment is initiated [II, B].[4] Furthermore, this strategy becomes of particular importance in clinical and survivorship care plans, to improve physical function in order to prevent disability and falls, especially in older adults.[2]

Acupuncture. A Cochrane review from 2017 stated that due to the limited data available, there is insufficient evidence to support or refute the use of acupuncture for neuropathic pain.[35] However, several recent randomised phase II studies are encouraging even if some trials are limited by their small sample size and short-term follow-up.[36−38] Specifically, the study by Bao et al.[38] ($n = 75$) incorporates a sham treatment and a nontreatment control to evaluate the efficacy of acupuncture for CIPN. Acupuncture resulted in a meaningful improvement in CIPN symptoms. Acupuncture might be considered in selected patients to treat CIPN symptoms [II, C].

Scrambler therapy. Scrambler therapy involves the use of a device to treat pain via noninvasive cutaneous electro-stimulation. This strategy was reported to be beneficial as a noninvasive method for some cancer patients in earlier pilot

Table 3. CIPN therapy: non-pharmacological interventions

Intervention	Comments	LoE/GoR	References
Acupuncture	Several recent randomised phase II studies are positive, Cochrane review from 2017: insufficient data for/or against a recommendation	II, C	36−38,96
Neurofeedback	Pilot study in 71 cancer survivors, potential benefit for EEG-based neurofeedback	II, C	43
Physical exercise	Several strategies are available: supervised medical exercise (sensorimotor function, endurance, strength of flexibility), self-management interventions (e.g. EXCAP©®)	II, B	4,20
Scrambler therapy	Noninvasive cutaneous electrostimulation	II, D	39,40
Self-guided online cognitive behavioural strategies	PROSPECT, pilot RCT ($n = 60$), greater improvements in 'worst' pain than usual care	II, C	41
Spinal cord stimulation	Small number case series, only in truly refectory pain due to CIPN, invasive and expensive procedure: electrode insertion into the dorsal re-entry zone of spinal cord and pulse generator implantation under the skin	V, C	42

CIPN, chemotherapy-induced peripheral neurotoxicity; EEG, electroencephalogram; EXCAP©®, Exercise for Cancer Patients; GoR, grade of recommendation; LoE, level of evidence; PROSPECT, Proactive Self-Management Program for Effects of Cancer Treatment; RCT, randomised controlled trial.

trials. However, the latest pilot randomised trial showed no beneficial effect of scrambler therapy.[39,40] Scrambler therapy is not recommended to treat CIPN [II, D].

PROSPECT. Proactive Self-Management Program for Effects of Cancer Treatment (PROSPECT) represents a self-guided, online cognitive and behaviourally-based pain management intervention for a period of 8 weeks in order to reduce pain deriving from CIPN.[41] A randomised pilot trial (*n* = 60) showed promising results. The intervention implies very little harm and, therefore, a weak recommendation in favour of a self-guided online cognitive and behaviour-based pain management seems to be rational [II, C].

Spinal cord stimulation. Spinal cord stimulation (SCS) represents a neuromodulation technique that is used to treat truly refractory neuropathic and sympathetically-mediated chronic pain. SCS is an invasive and expensive procedure as it involves percutaneous or surgical implantation of electrodes in the epidural space, with power supplied by an implanted battery. SCS has been reported to be successful in several cases; however, no RCT is available in patients with CIPN.[42] It may be discussed for selected patients, with truly refractory neuropathic pain and for whom conservative approaches failed [V, C].

Neurofeedback. A randomised pilot study in 71 cancer survivors suggests potential benefit for electroencephalo-gram (EEG)-based neurofeedback.[43] As the intervention implies very little harm, a weak recommendation in favour of neurofeedback is justified (generalisability is limited) [II, C].

Supportive measures for safety and self-management

Assistance with daily living, predominantly sensory damage. For the sensory nerve damage with corresponding impairment in the activities of daily living (ADL), the following assistance measures (described in supplementary Table S4, available at https://doi.org/10.1016/j.annonc.2020.07.003) can be helpful for the patient [V, B] and discussion with the physiotherapist about these measures can be very helpful.

Assistance with daily living, motor deficit. Problems arise with walking (specifically in the elderly), balance, driving, biking and standing still for extended time periods. Helpful strategies regarding risk assessment of falling, safety measures and supportive measures for ADL are shown in Table 4.

Patients and their caregivers may develop their own strategies to come to terms with the limitations. Support and information by health care professionals can enhance these, correct these if considered harmful and recommend other interventions that will fit the patients' ADL patterns. Rehabilitation medicine plays an important role in this setting, and consistency of the information available in the clinical setting from both physicians and nurses is important. Because most patients are now treated on an outpatient basis, caregivers should be included in the discussions and educational issues. The safety issues for both sensory

Table 4. Practical aspects, risk assessment of falling, safety measures and measures for ADL, predominantly motoric damage[97] (expert opinion)
Risk assessment of falling, particularly in elderly patients
• Observe patients at the clinical setting, for example, walking pattern (gait) when entering a room
• Use visual input to compensate for loss of lower extremity sensation in navigating changing terrain
• Patient reports losing balance
Safety measures
• Ensure enough light, also in stairwells and hallways
• Install handrails, also in the bathroom/shower area
• Check floor condition—slippery, uneven, loose rugs, stairs
• Clear corridors or rooms of clutter
• Use skid-free shower and bathroom mats
• Use a cane or walker if gait is unsteady
• Wear shoes that support and are skid-proof
• Employ special material for the kitchen (non-slip potholders), rubber gloves
• Caveat: Permission to drive must be discussed with the treating oncologist
Suggestions for assistance in ADL
• Encourage eye-hand contact when holding objects
• Hand and finger dexterity for computer operations, safety with tools (hand dexterity can be assessed easily with the Purdue Pegboard text)
• Help choose proper assistance object, adaptation to proper size
• Help choose tools for pulling on socks, shoes, zippers

ADL, activities of daily living.

and motor deficits should be addressed at an early stage of the treatment. A timeframe of how long the CIPN may last should be part of the information.

Safety and prevention information. Depending on the administered antineoplastic drug, safety and prevention information should be communicated to the patient before therapy starts (Table 5).

Particular attention must be paid to patients receiving oxaliplatin, as the corresponding acute neurotoxicity may include a very unpleasant hyperexcitability (sensitivity to cold) (supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2020.07.003). Information before the first application is of utmost importance as the potential

Table 5. Safety and prevention information (expert opinion)
General measures (sensory disturbances)
• Depending on the drug: application of warm or cold; avoid extreme temperatures
• Caution about exposure to temperature extremes (outdoor activities)
• Recommendations for clothing: warm shoes, socks and gloves, depending on sensation
• Caution for injury with sharp objects—when cutting nails, knives etc.
• Attention with infections—inflammation of nail cuticle (paronychia)
• Avoid pressure points, for example, tight shoes
• Teach patient the principles of foot care, including inspection of the feet for sores or blisters and the importance of wearing properly fitted shoes
• Caveat: Permission to drive must be discussed with the treating oncologist
Additional measures for patients receiving oxaliplatin
DO
• Wear gloves when removing food/objects from refrigerator or freezer
• Wear warm shoes and socks also at home unless floor heating available
• Protect ears and nose from cold; cover mouth with a scarf
AVOID
• Consuming cold food and drinks
• Contact with cold objects
• Breathing cold air
• Extended exposure to cold when activity is outdoors
• Holding metal railings, cold steering wheels

experience of laryngeal spasms and perceived dyspnoea can provoke panic attacks. Several helpful specific counselling measures are depicted in Table 5.

Ototoxicity

Ototoxicity is caused by peripheral damage of special sensory neurons in the cochlea. Cisplatin (this guideline focuses on cisplatin) is one of the most ototoxic agents, which is well known to cause irreversible damage to the outer hair cells of the cochlea, starting with the basal region.[44] This damage can result in a bilateral sensorineural hearing loss, affecting 20%–75% of patients.[45] Although cisplatin-induced hearing loss initially involves higher frequencies, it might eventually affect lower frequencies, particularly those critical for speech perception, if the more apical parts of the cochlea are damaged. Most patients experience some degree of tinnitus during cisplatin-based ChT, and about 40% of long-term survivors have reported tinnitus a median of 4–10 years after treatment.[46,47] Carboplatin (approximately 5% of patients) and vinca alkaloids can cause ototoxicity to a much lesser extent. Oxaliplatin very rarely causes ototoxicity.

Risk factors. Risk factors for developing ototoxicity include increasing cumulative cisplatin dose, application schedule (cisplatin 100 mg/m^2 over 5 days is better than over 3 days [I, A]), young age, concomitant applications of other ototoxic drugs (e.g. aminoglycosides and loop diuretics), preceding/concomitant radiotherapy to cochlea or cranial nerve VIII, impaired pre-exposure hearing ability, renal insufficiency and specific genetic variants (e.g. glutathione S-transferase genotypes and variants of *WFS1*) [III, B].[45,47]

Assessment/diagnosis. Before therapy with cisplatin starts, discussions with the patient should include questions related to their profession. If their livelihood is dependent on their hearing acuities, careful treatment planning is warranted. During treatment, patients should be encouraged to report first signs of hearing impairment, which often are noticed by the patients when using the telephone or when multiple persons are simultaneously speaking.

For early detection of ototoxicity in adults receiving platinum agents, a pure tone audiometry is recommended (including the wide spectrum of frequencies 500–8000 Hz) [IV, A]. A baseline assessment should be done before ChT and at the completion of therapy, at minimum [IV, B]; this recommendation refers specifically to patients with testicular cancer as almost all studies were done in this patient population.

Several grading systems for ototoxicity are available such as the Brock, American Speech-Language-Hearing Association (ASHA), Muenster, Chang, National Cancer Institute CTCAE (NCI-CTCAE), SIOP Boston and TUNE grading system.[48] Some are designed for use in children (Brock, Muenster, Chang, SIOP), others for adults (TUNE) and some for both (ASHA and NCI-CTCAE). There is substantial variability in the definition of the grades among the scales. No

recommendation on the optimal tool is possible; however, the ASHA definition of hearing loss seems to overestimate the hearing problem and may rather not be used as a clinical tool.[47]

Prevention. Brock et al.[49] reported that the addition of sodium thiosulfate to cisplatin in children with localised hepatoblastoma led to a lower incidence of cisplatin-induced hearing loss without jeopardising survival. A second phase III trial confirmed this protective effect by sodium thiosulfate against cisplatin-induced hearing loss in children,[50] but a lower survival rate was seen in the subgroup of patients with disseminated disease. This observation might suggest that sodium thiosulfate is tumour protective in addition to being otoprotective in certain patients. Although otoprotective treatment with sodium thiosulfate could offer a significant patient benefit, it cannot currently be recommended as standard treatment, due to the uncertainty regarding a possible tumour protection and lack of evidence among adult cancer patients [I, C].

None of the other numerous potential otoprotective agents, namely amifostine, aspirin, curcumin, D- or L-methionine, glutathione ethyl ester, alpha-lipoic acid, methylthiobenzoic acid, tiopronin, melatonin, N-acetylcysteine, intratympanic dexamethasone, pantoprazole, resveratrol and vitamin E, can be recommended for the prevention of cisplatin ototoxicity [II, D]. They were shown not to be beneficial or the qualities of the studies were not adequate enough to draw any final conclusions.

At this point, no recommendation in favour of pharmacogenomics testing in routine practice is possible [III, A].[51]

Treatment. No causative treatment strategy is available so far. Hearing aids can be of help. Patients with profound hearing loss may benefit from cochlear implants. Further assistive devices (e.g. auditory trainers, telephone amplifiers) can be beneficial as well.[48]

Apart from hearing loss, patients frequently suffer from continuous tinnitus with unpredictable outcome in the sense of remission. For patients suffering from tinnitus, cognitive behavioural strategies (CBT) might be offered [V, B].[52] Various suggestions for diminishing acoustic stimulus can be found in supplementary Table S5, available at https://doi.org/10.1016/j.annonc.2020.07.003.

Recommendations

- Regular assessment of CIPN should be done as it enables the health care professionals to discover potential symptoms early, before the neuropathy becomes irreversible [IV, A].
- No effective drug exists to prevent CIPN [II, D–I, E].
- Cryotherapy with, for example, frozen socks and gloves can be considered (most evidence is available for taxane therapy) [II, C].
- Compression therapy using surgical gloves to prevent CIPN can be considered [III, C].

- Medical exercise to improve muscular strength and sensorimotor functions can be offered to patients at risk of developing CIPN [II, C].
- When patients experience chronic CIPN, treatment approaches should focus on reduction or relief of neuropathic pain [IV, A].
- Duloxetine is the only agent recommended with level I evidence for the treatment of neuropathic pain [I, B].
- Venlafaxine, pregabalin, amitriptyline, tramadol or strong opioids can be considered for the treatment of neuropathic pain [II, C].
- As a local intervention, topical low-concentration menthol cream should be considered in patients with CIPN [III, B].
- Physical exercise and functional training (e.g. vibration training) reduces CIPN symptoms and is, therefore, recommended [II, B].
- Acupuncture might be considered in selected patients to treat CIPN symptoms [II, C].
- For early detection of ototoxicity in adults receiving platinum agents, a pure tone audiometry is recommended (including the wide spectrum of frequencies 500—8000 Hz) [IV, A].
- Prophylactic treatment with sodium thiosulfate could offer a significant patient benefit; however, it cannot currently be recommended as standard treatment, due to the uncertainty regarding a possible tumour protection and lack of evidence among adult cancer patients [I, C].

CENTRAL NEUROTOXICITY

For many antineoplastic drugs, the toxicity is related to the route of administration and cumulative dose, and can vary from brief, transient episodes to more severe, chronic sequelae.[53] The so-called 'oncobrain' or 'chemobrain' for which a substantial amount of research is ongoing will not be addressed in this guideline.

Encephalopathy

This term is widely used to describe global cerebral dysfunction in the absence of primary structural brain disease. In this guideline, only acute encephalopathy will be discussed. Most clinical features of acute encephalopathy are nonspecific, and do not reliably identify a particular aetiology. In cancer patients, its occurrence has been associated with classic chemotherapeutics (supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2020.07.003). Beside these toxic causes, acute encephalopathy may be facilitated by concomitant septic disease, preexistent leukoencephalopathy and metabolic changes (e.g. sodium disturbances due to cancer-related syndrome of inadequate antidiuretic hormone release). Clinical features of acute encephalopathy include changes in consciousness (from impaired attention to confusion and delirium with psychotic symptoms), decreased consciousness (from drowsiness to coma) and changes in affect (apathy, anxiety,

agitation). The presentation of acute encephalopathy may also include focal signs like paresis, speech disorders, seizures and cranial nerve dysfunctions. An intensified, diagnostic procedure is necessary if the clinical picture exaggerating these phenomena (mentioned above) and differential diagnoses such as cerebral bleeding or ischaemia in risk patients (e.g. history of thromboembolic event or current anticoagulation) should be radiologically ruled out as well as leptomeningeal disease. In case of unexplained accompanying fever and meningeal irritation, an infectious cause should also be ruled out by cerebrospinal fluid (CSF) examination [V, B].

Ifosfamide-induced acute encephalopathy. The estimated incidence for ifosfamide-induced acute encephalopathy is shown in supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2020.07.003. Risk factors for the development of an acute encephalopathy may include: dose of ifosfamide, drug interactions (CYP2B6 inhibitors), renal impairment, low serum albumin, bulky abdominal disease and prior cisplatin treatment [V, B].[54] In some case reports, the concomitant use of aprepitant was thought to be a risk factor of developing an ifosfamide-induced acute encephalopathy. This assumption could not be confirmed in larger reported series.[54—56]

Prevention and treatment. As prophylactic or therapeutic measures, methylene blue and/or thiamine and/or glucose 5% have been applied in small series.[57—59] No controlled trials are available for these agents and the possibility of spontaneous resolution of encephalopathy should be taken into account. Some cases have shown some benefit of methylene blue; however, several retrospective studies on the prophylactic usage of methylene blue, combined with thiamine, do not support its efficacy.[57] Furthermore, methylene blue may induce a serotonin syndrome.[60] Methylene blue and/or thiamine and/or glucose 5% are not recommended for the prevention and treatment of ifosfamide-induced acute encephalopathy [V, D]. The prophylactic use of exogenous albumin administration is also not effective and is not recommended [V, D].[61]

The treatment is purely symptomatic and includes discontinuation of ifosfamide, correction of electrolytes (if imbalanced) and symptomatic treatment with, for example, benzodiazepines [V, B]. In almost all cases, a spontaneous full remission can be seen without sequelae.

Posterior reversible encephalopathy syndrome

Patients present with acute neurological deficits including altered consciousness, visual disturbances, blindness, headaches and seizures. Posterior reversible encephalopathy syndrome (PRES) is rare but increasingly diagnosed (supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2020.07.003). A disruption of the blood—brain barrier due to endothelial injury by abrupt blood pressure changes leads to typical vasogenic oedema.[53] The posterior regions of the brain are most susceptible to injury because of reduced sympathetic innervation and

autoregulation of blood pressure. Therefore, the oedema, which may be demonstrated on T2-weighted magnetic resonance imaging (MRI) scan hyperintensities, involves bilateral parietal-occipital lobes and predominates in white more than grey matter. Risk factors include pre-existing arterial hypertension, renal impairment, autoimmune diseases, high-dose antineoplastic therapy, allogenic stem-cell transplantation, solid organ transplantation and immunosuppression (e.g. ciclosporin) [V, B].[62]

Prevention and treatment. Very stringent control of blood pressure is crucial, especially when PRES is present [V, B]. Treatment requires cessation of anticancer therapy and antiepileptic treatment in case of seizures [V, B]. PRES is usually reversible with appropriate supportive management within 2 weeks.[63] A reintroduction of the prior anticancer therapy has to be decided on an individual basis.

Acute cerebellar syndrome

Cerebellar syndrome may develop in patients receiving, for example, high-dose cytarabine. Other examples, however very rare, include bortezomib, rituximab and trastuzumab. It is characterised by dizziness, ataxia, dysarthria, vertigo with nausea and vomiting and cerebellar or vestibulocochlear eye movement disorders usually manifesting 2 to 5 days after treatment initiation. In addition to careful history-taking and neurological examination, a T2-weighted MRI scan demonstrating cerebellar hyperintensities and CSF excluding central nervous system (CNS) infection will help to find the diagnosis.[53] Risk factors may include liver and renal impairment, very high antineoplastic drug doses and age >40 years [V, B].

Prevention and treatment. No specific preventive measure or causative treatments are available.[64] Certainly, the causing antineoplastic drug should be stopped. In case of cytarabine treatment, avoidance of very high doses of cytarabine if possible, especially in patients with renal impairment [IV, C]. This might lower the incidence of an acute cerebellar syndrome. Recovery is uncertain, including remission and persistence of disabling ataxia in sitting and walking.

Myelopathy

Transverse myelopathy may develop due to high antineoplastic drug levels in CSF for at least 24 h. It is an uncommon complication, but may appear in patients after intrathecal (IT) methotrexate (MTX), cytarabine, cisplatin, carmustine and thiotepa treatment administered via the lumbar route.[65] Patients suffer from back or leg pain followed by paraparesis or more often paraplegia, sensory loss and sphincter dysfunction. T2-weighted MRI images may demonstrate lesions in the dorsal column of the spinal cord. According to meningeal irritation, symptoms of aseptic meningitis may be present. Risk factors include concurrent craniospinal radiotherapy and frequent injections via the lumbar route.

Prevention and treatment. No evidence-based preventive measure is established. For treatment, steroids injected slowly via the lumbar route might be considered, although sufficient data are limited [V, C].[53] Treatment with high-dose folate metabolites in patients with MTX-induced myelopathy may be worth a try [V, C].[66] In general, recovery is variable; the majority of patients show clinical improvement.

Progressive multifocal leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) is a very rare, devastating demyelinating disease of the CNS, which almost exclusively occurs in patients with compromised immune systems (mainly CD4 or CD8 immunosuppression). The prevalence of PML is estimated to be 0.07% among patients with haematological malignancies. PML has been rarely reported in patients with an underlying haematological malignancy treated with immunomodulatory drugs or with antibodies.[67] Subacute neurological symptoms in a patient at increased risk of PML, along with typical MRI findings and detection of John Cunningham virus (JCV) DNA in the CSF are sufficient for diagnosis. In the absence of an effective prevention or specific treatment of PML, no recommendation is possible. The main approach is restoring the host adaptive immune response, a strategy that appears to prolong survival and may minimise CNS injury and avoid severe disability.[53,67]

Aseptic meningitis

Occurrence of aseptic meningitis is typically associated with IT administration of chemotherapeutics and may be seen in 10%—50% of patients being treated with MTX and specifically liposomal cytarabine (liposomal cytarabine is permanently discontinued due to product-specific supply issues) (supplementary Table S6, available at https://doi.org/10.1016/j.annonc.2020.07.003).[68] Typically, signs of meningeal irritation (headache, nuchal stiffness, vomiting, fever, lethargy) develop within 2—4 h after drug injection and usually last for about 12—72 h. This is the distinguishable criterion from iatrogenic bacterial infection, which is usually also accompanied by fever. Symptoms resolve spontaneously with symptomatic treatment. CSF examination may show pleocytosis without other features of bacterial infection.[69] CSF culture should be carried out for differential diagnosis. Although little evidence is available, sufficient clinical consensus is present for the concomitant use of IT corticosteroids (the most often used dose is 4 mg IT dexamethasone) to gradually prevent aseptic meningitis [V, C].

Stroke and vasculopathy

There is an increased risk of thromboembolic stroke in, for example, platinum-based ChT as well as, less often, in 5-fluorouracil, gemcitabine and bleomycin treatment. In addition, angiogenesis inhibitors may induce an ischaemic stroke.[70] Risk factors include radiotherapy-induced

vasculopathy as well as prothrombotic activity of cancer itself.

Recommendations

- As prophylactic or therapeutic measures, methylene blue and/or thiamine and/or glucose 5% cannot be recommended [V, D].
- The prophylactic use of exogenous albumin administration is not recommended [V, D].
- The treatment is purely symptomatic and includes discontinuation of ifosfamide, correction of electrolytes (if imbalanced) and symptomatic treatment with, for example, benzodiazepines [V, B].
- Very stringent control of blood pressure is crucial, especially when PRES is present [V, B].
- Treatment of PRES requires cessation of anticancer therapy and antiepileptic treatment in case of seizures [V, B].
- For acute cerebellar syndrome, no specific preventive measure or causative treatment is available.
- To avoid myelopathy, no evidence-based preventive measure is established.
- For treatment of myelopathy, steroids might be considered, although sufficient data are sparse [V, C].
- Treatment of myelopathy with high-dose folate metabolites in patients with MTX-induced myelopathy may be worth a try [V, C].
- In the absence of an effective prevention or specific treatment of PML, no recommendation is possible. The main approach is restoring the host adaptive immune response.
- Sufficient clinical consensus is present for the concomitant use of IT corticosteroids (the most often used dose is 4 mg IT dexamethasone) to gradually prevent aseptic meningitis [V, C].

METHODOLOGY

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development https://www.esmo.org/guidelines/esmo-guidelines-methodology. The relevant literature has been selected by the expert authors. Levels of evidence and grades of recommendation have been applied using the system shown in supplementary Table S7, available at https://doi.org/10.1016/j.annonc.2020.07.003.[98] Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

DISCLOSURE

BJ has reported advisory board and/or honoraria for presentations for Alexion Pharmaceuticals, Temmler (Hormosan Pharma), Novartis, Biomarin, Merz Pharmaceuticals, Ipsen Pharma and Allergan; FC has reported consultancy role for Amgen, Astellas/Medivation, AstraZeneca, Celgene, Daiichi-Sankyo, Eisai, GE Oncology, Genentech, GlaxoSmithKline, MacroGenics, Medscape, Merck-Sharp, Merus BV, Mylan, Mundipharma, Novartis, Pfizer, Pierre Fabre, prIME, Roche, Sanofi, Seattle Genetics and Teva; GC has reported financial interests, honoraria for speaker, consultancy or advisory role and/or institutional research funding from Toray, Disarm, Helsinn, PledPharma, Mundipharma, Kedrion and Chiesi; PJ has reported travel support from Helsinn, consulting or advisory role for Bristol-Myers Squibb, Chugai, Norgine, Helsinn and Clinigen and research grant from Chugai; ELR has received research grants from Mundipharma and Amgen, honoraria for lectures or advisory board from Tocagen, AbbVie, Daiichi Sankyo, Mundipharma and Novartis; MP has received honoraria for lectures, consultation or advisory board participation from Bristol-Myers Squibb, Novartis, Gerson Lehrman Group, CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, AstraZeneca, AbbVie, Lilly, MEDahead, Daiichi Sankyo, Merck Sharp & Dohme and has reported research funding from Bristol-Myers Squibb, Böhringer-Ingelheim, GlaxoSmithKline, Merck Sharp & Dohme and Roche; FS has reported financial interests, honoraria for speaker, consultancy or advisory role, royalties, direct research funding from Tesaro, Helsinn, Vifor, Merck Sharp & Dohme, Roche, Amgen, Pierre Fabre Oncology, Pfizer, Leo Pharma, Arrow and Bristol-Myers Squibb; KJ has reported financial interests, honoraria for speaker, consultancy or advisory role, royalties and direct research funding from Merck Sharp & Dohme, Merck, Amgen, Hexal, Riemser, Helsinn, Tesaro, Kreussler, Voluntis, Pfizer, POMME-med, PharmaMar, prIME Oncology and Onko Solutions; all remaining authors have declared no conflicts of interest.

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