is deemed to be appropriate by the treating surgeon then it
deed should be carried out in an extended fashion. Moreover,
we believe as others [11, 12] that there is very possibly a
therapeutic advantage. However, at minimum, better staging
helps us to better select those patients who may benefit from
adjuvant therapy as well as enrolling into vital clinical trials.
Additionally, the template described in this article is easily
reproduced with a robotic approach [13].

In conclusion, extended lymph node dissection should be
carried out in all patients, where a lymph node dissection is
deemed to be appropriate. However, this quandary will continue
until new technologies such as RT–PCR or imaging such as
lymphangiography enhance MRI becomes validated and
incorporated to enhance our current prediction tools. Finally, if
there is a question about whether or not to carry out a lymph
node dissection than one should critically evaluate whether or not
radical prostatectomy is indeed appropriate in the first place.

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Prevention of chemotherapy-induced peripheral neuropathy: a matter
of personalized treatment?

Peripheral neuropathy is a frequently occurring side-effect of
neurotoxic chemotherapy, negatively influencing the quality of
life of cancer patients [1–3]. Platinum analogues and antitubulins
are among the most feared agents in this respect [4, 5].

Development of chemotherapy-induced peripheral neuropathy (CIPN) also frequently has its impact on anticancer
therapy, leading to dose reduction or discontinuation of
neurotoxic treatment. Preventive measures to abolish or
decrease CIPN are currently scarce, and not routinely used in
clinical oncology practice, perhaps with the exception of Ca–Mg
infusions before and after oxaliplatin treatment [6, 7].

Patient-related predisposing factors like higher age, pre-
exiting neuropathy and concomitant disease such as diabetes
mellitus may contribute to the development of CIPN [8].

Treatment-related factors such as cumulative dose, dose
intensity and pharmacokinetics are influential as well [9].
However, interindividual variability in toxicity and response to
treatment is an important problem in clinical practice: in fact,
we are not able to predict which of the patients are likely to
develop CIPN. Genetic factors might be of importance in this
respect [10]. However, literature data on the topic of
pharmacogenomics in the development of CIPN are
inconsistent so far [11].

In this issue of Annals of Oncology, Hertz et al. describe a very
interesting pharmacogenomic approach with the potential of
CIPN prevention in breast cancer patients treated with
paclitaxel (Taxol) [12].

Paclitaxel is primarily metabolized by CYP2C8, and exposure
to paclitaxel in cancer patients is correlated with CYP2C8
activity. Single-nucleotide polymorphisms in the CYP2C8, such as the *3(rs11572080 R139K and rs10509681 K339R) variant,
influence paclitaxel metabolism, leading to increased drug
exposure [12]. In recent studies, the CYP2C8*3 variant was

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reported to lead to increased paclitaxel-induced peripheral neuropathy [13–15]. Breast cancer patients carrying the CYP2C8*3 variant were also more likely to achieve clinical complete response from neoadjuvant paclitaxel treatment [15].

In the current, larger study, 411 paclitaxel-treated patients were eligible for CYP2C8*3 genotype analysis. As hypothesized, the risk of paclitaxel-induced peripheral neuropathy was highest in patients who were homogenous for the CYP2C8*3 variant, and lowest in patients homogenous for the wild-type allele (overall log-rank $P = 0.006$). Using the entire cohort, each CYP2C8*3 allele approximately doubled the risk for grade 2+ (NCI CTCAE criteria) neuropathy. Furthermore, non-European-American patients were at higher risk than European-American patients of a similar genotype ($P = 0.030$). The authors conclude that patients who are known to carry CYP2C8*3, and particularly those known to be homogenous, should be assumed to be at increased risk of paclitaxel-induced peripheral neuropathy. Furthermore, beyond CYP2C8 genotype, non-European individuals were at an increased risk of developing CIPN in this study [12].

Importantly merits of the current study are the single genotype–phenotype association that was selected a priori, and the fact that almost all patients were treated with paclitaxel only. Most other studies in this field used patient populations treated with a combination of potential neurotoxic chemotherapies and/or a hypothesis-generating pharmacogenomic approach, potentially underestimating the role of single polymorphisms. For instance, Marsh et al. [16] could not demonstrate reproducible significant associations between the genotype (27 selected polymorphisms) and the outcome or toxicity in a large study of ovarian cancer patients ($n = 914$) treated with platinum plus taxane chemotherapy.

A limitation of the study by Hertz et al. [12] is its retrospective nature, leading to differences in paclitaxel treatment and schedule, and potentially leading to non-uniform (neuro)toxicity data collection. Quite rightly, the authors propose to organize a prospective trial to substantiate their findings, and to demonstrate the clinical utility of individualizing paclitaxel therapy based on CYP2C8 genotype profiling [12].

In general, a pharmacogenomic approach with the potential of identifying patients with a high risk of neurotoxicity development to a given chemotherapeutic agent is rather intriguing. Variants in genes relevant to drug disposition, metabolism and drug action can influence the patient’s exposure and sensitivity to the drug [15]. For paclitaxel, most studies focus on mutations in biologically relevant candidate genes such as CYP2C8, CYP3A4, CYP3A5 and ABCB1 [11, 15]. For several other neurotoxic agents (e.g. carboplatin, vincristine, thalidomide, oxaliplatin, cisplatin), positive associations have been found between CIPN development and genotype. However, other studies—partly with similar chemotherapeutic agents and genes tested—failed to show positive associations between the genotype and risk of CIPN development. As such, data are still inconclusive with regard to the potential role of pharmacogenomics in the risk management of CIPN [11].

Also for non-neurological chemotherapeutic-induced toxicity, genotyping has been studied in terms of risk management. A recent study demonstrated the clinical value of prospective screening for dihydropyrimidine dehydrogenase deficiency, reducing the risk of severe toxicity (diarrhea) in advanced colorectal cancer patients treated with capecitabine [17].

To further address the value of pharmacogenomic approaches for the optimization of patient care in terms of CIPN prevention in cancer therapy, several suggestions are proposed [11, 12]. First, only specific genes that have been associated with CIPN course and severity should be studied in such a clinical study. As such, candidate genes of interest are to be identified beforehand. Second, strict and well-defined inclusion criteria should be used in future studies. Ideally, only similar chemotherapeutic regimens for a specific indication/type of malignancy should be formulated. A combination of neurotoxic anticancer agents is potentially of less value in this respect than neurotoxic monochemotherapy. Third, such a study protocol should be strict with regard to the stratification for potential other CIPN risk factors, such as diabetes mellitus, age, alcohol intake, concurrent medication and symptomatic treatment.

Lastly, the method leading to clinical assessment of CIPN severity is of pivotal importance, and should be described in detail beforehand. In everyday clinical practice, the assessment of CIPN is difficult, and differs among physicians in the field of oncology and neurology. The NCI-CTC criteria are used preferentially in oncology trials, whereas neurologists usually carry out neurological examinations, and score CIPN according to (sub)clinical neuropathy scales such as the total neuropathy score [18, 19]. Furthermore, interobserver variability is a potential pitfall in grading of CIPN severity [20]. Currently, the optimal way of sufficiently describing the clinical burden of CIPN is still a matter of debate: e.g. inclusion of clinical versus subclinical measures, and inclusion and choice of physician versus patient reported outcome measures [21–23].

Recently, a unique multidisciplinary, multicenter collaboration has been achieved in order to study and optimize outcome measures in CIPN: the CI-PERINOMS study group [24]. The CI-PERINOMS group studies and compares several outcome measures in CIPN, in order to facilitate CIPN assessment. The first step towards this goal has been published recently [25]. Additional studies are foreseen shortly. As for now, a combination of clinical, physician-driven and patient reported outcome measures is potentially the most optimal way to assess CIPN [25].

The combination of the use of sound, validated outcome measures for CIPN in future prospective, clinical trials with optimal inclusion criteria for chemotherapy, cancer population and pharmacogenomic approach will surely increase our knowledge of the genetic role in CIPN development. As such, a step forward towards personalized treatment could be achieved, ultimately leading to the prevention of CIPN.

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