Peripheral Neuropathy Induced by Microtubule-Stabilizing Agents

James J. Lee and Sandra M. Swain

Abstract

Microtubule-stabilizing agents (MTSAs), including the taxanes and epothilones, are effective chemotherapeutic agents for the treatment of many cancers. Neuropathy is a major adverse effect of MTSAs, with severe peripheral neuropathy (grade 3 or 4) occurring in as many as 30% of patients treated with a MTS. MTS-induced neuropathy usually resolves gradually after cessation of the treatment. The most reliable method to accurately assess MTS-induced neuropathy is by clinical evaluation, although additional techniques are being developed and evaluated. Among MTS-induced neuropathy, the most extensively studied is that induced by taxanes; such a neuropathy usually presents as sensory neuropathy and is more common with paclitaxel than docetaxel. The incidence of MTS-induced neuropathy seems to depend on the MTS dose per treatment cycle, the schedule of treatment, and the duration of the infusion. Although there have been several small clinical trials with neuroprotective agents, early recognition and supportive care are the best approaches for prevention and management of MTS-induced neuropathy. In the future, research should focus on elucidating the mechanism of MTS-induced neuropathy, developing reliable in vivo and in vitro preclinical models to study MTS-induced neuropathy, developing a more reliable grading system for MTS-induced neuropathy, evaluating the efficacy of potential neuroprotective agents in clinical trials.

Introduction

Microtubule-stabilizing agents (MTSAs), including the taxanes and epothilones, stabilize microtubules, block mitosis, and induce cell death. Taxanes include polyoxyethylated castor oil–based paclitaxel, docetaxel, and ABI-007 and are effective chemotherapeutic agents for various cancers. ABI-007 is a new polyoxyethylated castor oil–free formulation of paclitaxel with good antitumor activity in phase III clinical trials of breast cancer. Epothilones are newly emerged MTSAs in active clinical trials and include ixabepilone (BMS-247550), BMS-310705, patupilone (EPO906), epothilone D (KOS-862), and ZK-EPO. A major toxicity associated with MTSAs, including the taxanes and epothilones, is peripheral neuropathy (PN). Severe PN (National Cancer Institute [NCI] Common Toxicity Criteria grade 3 or 4) occurs more frequently in paclitaxel-based chemotherapy than in docetaxel-based chemotherapy (Tables 1 and 2). A clinical assessment, including a physical examination, is currently the most reliable method to assess MTS-induced PN because we lack more reliable objective methods. Although neuroprotective agents such as amifostine have been evaluated in clinical trials, no neuroprotective agent has performed better than early recognition and supportive care.

Preclinical Investigations on the Mechanism of MTS-induced Neuropathy

PN is caused by morphologic or functional abnormalities in peripheral nerves and is separated into axonopathy (axon abnormalities) or myelopathy (myelin sheath abnormalities). MTS-induced PN presents as axonopathy or axonopathy plus myelopathy. The mechanism of MTS-induced PN is unclear. However, because the survival and function of neurons require that proteins and other components be actively transported along long axons from a neuron’s cell body to its distal synapses, MTS treatment likely interrupts this active transport.

Addition of paclitaxel (10 μg/mL) to dorsal root ganglia cell cultures inhibited anterograde axonal transport, which was reversible and did not damage cells. Also, incubation of rat sciatic nerve with paclitaxel 200 μmol/L induced vesicle accumulation on both proximal and distal sides of the nerve, indicating that paclitaxel treatment blocked fast axonal transport. In another study involving rats, injection of paclitaxel into neurons induced microtubule transport inhibition.
aggregation without degenerative changes in peripheral nerves; microtubules aggregated first in Schwann cells and then in axons. Finally, systemic paclitaxel injection of rats induced microtubules accumulation in Schwann cells and axons but caused minimal damage to their sciatic nerve. Microtubule aggregation was not observed in sural nerve biopsies from patients with MTSA-induced neuropathy. Thus, the mechanism of MTSA-induced neuropathy remains unclear.

INCIDENCE AND RISK FACTORS OF MTSA-INDUCED NEUROPATHY

The incidence of MTSA-induced PN depends on risk factors including dose per cycle, treatment schedule, duration of infusion, cumulative dose, and comorbidity such as diabetes. Associations between these risk factors and the incidence of MTSA-induced PN have been confirmed in clinical trials, as discussed below. Although the clinical response of tumors to a specific MTSA is the most important reason to select a chemotherapy regimen, it is also prudent to evaluate the risk of developing PN associated with each chemotherapy regimen, especially for patients already at high risk of neuropathy.

Dose per Cycle

The incidence of PN depends on the dose of MTSA per treatment cycle. In a randomized study of paclitaxel in breast cancer, severe PN (WHO grade 3 or 4) was observed in 7% of patients receiving paclitaxel at 175 mg/m² but in only 3% of patients receiving paclitaxel at 135 mg/m². In the Cancer and Leukemia Group B (CALGB) 9342 trial, grade 3 or 4 sensory PN was observed in 33% of patients receiving paclitaxel at 250 mg/m² (n = 149), in 19% of patients receiving paclitaxel at 210 mg/m² (n = 152), and in 7% of patients receiving paclitaxel at 175 mg/m² (n = 150; P = .0001). In a phase II trial of breast cancer, grade 3 or 4 sensory PN was observed in 4% of patients receiving ABI-007 at 100 mg/m² weekly (n = 106) and in 17% of patients receiving ABI-007 at 125 mg/m² weekly (n = 75).
infusion of polyoxyethylated castor oil–based paclitaxel 100 mg/m². There was no significant difference in the peak concentration of total paclitaxel, unbound paclitaxel, and polyoxyethylated castor oil between patients with and without PN. However, the duration of the time of total paclitaxel above the concentration of 0.05 μmol/L was the most important pharmacokinetic risk factor for the development of PN (relative risk = 18.43; P = .036).

In the National Surgical Adjuvant Breast and Bowel Project B-26 trial of breast cancer, grade 3 or 4 PN was observed in 22% of patients receiving a 3-hour infusion of paclitaxel (250 mg/m²/cycle; n = 279) and in 13% of patients receiving a 24-hour infusion (n = 284). In a randomized phase III trial of paclitaxel (135 or 175 mg/m²) in patients with ovarian cancer, there was no significant difference in the incidence of grade 3 or 4 PN between the 3-hour (n = 187) and 24-hour (n = 204) infusion (0.7% vs 0.6%, respectively). Cumulative Dose

The onset of PN generally depends on the cumulative dose of MTSAs. In a randomized phase III study comparing docetaxel 100 mg/m² every 3 weeks (n = 225) with paclitaxel 175 mg/m² every 3 weeks (n = 224) in metastatic breast cancer, the mean cumulative dose to onset of grade ≥ 2 PN was 371 mg/m² for docetaxel and 715 mg/m² for paclitaxel. In patients treated with ixabepilone (every 3 weeks or daily × 5 every 3 weeks), the median onset of grade ≥ 2 PN occurred after five to six cycles.

Other Risk Factors

Other risk factors may include diabetes mellitus, concurrent administration of cisplatin, or age with limited data. PN is a major complication of diabetes mellitus, and grade 3 or 4 sensory neuropathy has been reported in diabetic patients with cancer who were treated with high-dose paclitaxel. In a retrospective analysis of paclitaxel-induced PN in 18 diabetic patients, neuropathic symptoms were exacerbated in 50% of patients; these symptoms then worsened in 11% of these patients to grade 3 neuropathy.

Because platinum compounds induce PN, the possibility that coadministration of platinum compounds increased the incidence of MTSAs-induced PN was examined in a phase III trial, in which 327 patients were randomly assigned either to paclitaxel (175 mg/m²) and carboplatin every 3 weeks or to paclitaxel (175 mg/m²) and epirubicin every 3 weeks. Results showed that grade 3 or 4 PN occurred in 2.5% of patients in both groups. However, a smaller prospective analysis of neurotoxicity of combined paclitaxel and cisplatin treatment in 21 patients with solid tumors found that patients with pre-existing neuropathy experienced more grade 3 or 4 PN earlier in the treatment and at a lower cumulative paclitaxel dose (<600 mg/m²) than patients without pre-existing neuropathy.

Older patients are more prone to MTSAs-induced PN. In a phase II trial of paclitaxel (150 mg/m² weekly), age was significantly associated with neurotoxicity during cycle 2 (P = .008). There has been interest in various genetic predispositions for neuropathy, such as Wlds (slow Wallerian degeneration gene) or CYP3A genotypes.

Clinical Assessment

Symptoms. Accurate information must be ascertained on the onset, distribution, and severity of neuropathic symptoms and on their interference of daily activities. Sensory neuropathy presents as paresthesia, numbness, and pain in the feet and hands, with symptoms generally appearing in the toes and then in the fingers. Paresthesia occurs in distal lower extremities with a glove-and-stocking
distribution and is most severe on planter surfaces. The severity of most symptoms is mild to moderate, and symptoms generally disappear on cessation of therapy. Acute tingling in fingertips and toes may occur within 24 hours after paclitaxel infusion. Paroxysmal pain reaction seems mainly to involve muscles and bones of lower extremities and usually occurs 2 to 4 days after paclitaxel infusion. Motor neuropathy is usually mild and presents as muscle weakness such as foot drop or difficulty in climbing stairs. Fine motor skills (e.g., buttoning a shirt or putting on earrings) may be diminished.

**Physical examination.** The first sign of sensory neuropathy is an elevated vibratory perception threshold in distal extremities and is often associated with loss of pain and temperature sensation. The vibratory perception threshold increases more in feet than in hands. The sense of position is usually lost in grade 3 or 4 neuropathy. MTSA-induced neuropathy is frequently manifested by decreased deep-tendon and ankle reflexes. Motor neuropathy presents as muscle wasting, weakness, and fasciculation.

**Neuropathy grading.** Neuropathy is graded by subjective complaints of patients and physical examinations by clinicians. The most widely used grading systems are the NCI Common Toxicity Criteria and WHO criteria (Table 3). The use of subjective patient complaints to assess neuropathy introduces large variations between assessments, and because clinical examinations depend on patient cooperation, this method is not entirely objective. Although these grading systems have been widely used, limitations result from intra- and interobserver variation and from the inconsistent interpretation of components of these grading systems (Table 4).

**Questionnaire**

Certain chemotherapy-induced toxicities (e.g., pain or discomfort) cannot be measured objectively but have a high impact on quality of life (QOL) and treatment decisions. Questionnaires assess symptoms via patient-based measurements of chemotherapy-induced toxicities, and their analyses can help to determine the impact of such toxicities on QOL. The Functional Assessment of Cancer Therapy–Taxane system and European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 are self-reporting instruments that measure health-related QOL in patients receiving chemotherapy. These questionnaires query physical, social, emotional, and functional well-being including neurologic symptoms. These systems have been validated in randomized trials. Thus, a questionnaire-based assessment of symptoms may be useful for measuring subjective MTSA-induced symptoms.

**Quantitative Sensory Testing**

Quantitative sensory testing (QST) is used to overcome interobserver discordance when assessing neurologic dysfunction. It measures the sensory threshold for a particular stimulus, such as vibration, by delivering a stimulus many times at various intensities via a specific algorithm. A prospective analysis of paclitaxel-induced neuropathy investigated the utility of QST to assess chemotherapy-induced neuropathy. The most sensitive test of QST was the vibration threshold of great toes, but QST was less sensitive for diagnosis of PN than clinical assessment. Although QST is relatively simple, noninvasive, and easily repeated, it may not have significant advantage to assess MTSA-induced neuropathy.

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**Table 3. Peripheral Neuropathy Grading Systems**

<table>
<thead>
<tr>
<th>Type</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NCI-CTC version 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor</td>
<td>Subjective weakness but no objective findings</td>
<td>Mild objective weakness interfering with function but not interfering with activities of daily living</td>
<td>Objective weakness interfering with activities of daily living</td>
<td>Paralysis</td>
</tr>
<tr>
<td>Sensory</td>
<td>Loss of DTRs or paresthesia (including tingling) but not interfering with function</td>
<td>Objective sensory loss or paresthesia interfering with function but not interfering with activities of daily living</td>
<td>Sensory loss or paresthesia interfering with activities of daily living</td>
<td>Permanent sensory loss interfering with function</td>
</tr>
<tr>
<td><strong>NCI-CTC version 3</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Motor</td>
<td>Asymptomatic, weakness on examination/testing only</td>
<td>Symptomatic weakness interfering with function but not interfering with activities of daily living</td>
<td>Weakness interfering with activities of daily living; bracing or assistance to walk (e.g., cane or walker) indicated</td>
<td>Life threatening; disabling (e.g., paralysis)</td>
</tr>
<tr>
<td>Sensory</td>
<td>Asymptomatic; loss of DTRs or paresthesia but not interfering with function</td>
<td>Sensory alteration or paresthesia interfering with function but not interfering with activities of daily living</td>
<td>Sensory alteration or paresthesia interfering with activities of daily living</td>
<td>Disabling</td>
</tr>
<tr>
<td><strong>WHO</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paresthesias and/or decreased DTRs</td>
<td>Severe paresthesias and/or mild weakness</td>
<td>Intolerable paresthesias and/or marked motor loss</td>
<td>Paralysis</td>
<td></td>
</tr>
<tr>
<td>ECOG</td>
<td>Decreased DTRs; mild paresthesias; mild constipation</td>
<td>Absent DTRs; severe paresthesias; severe constipation; mild weakness</td>
<td>Disabling sensory loss; severe peripheral nerve pain; obstipation; severe weakness; bladder dysfunction</td>
<td>Respiratory dysfunction secondary to weakness; obstipation requiring surgery; paralysis confining patient to bed/wheelchair</td>
</tr>
</tbody>
</table>

Abbreviations: NCI-CTC, National Cancer Institute Common Toxicity Criteria; DTR, deep tendon reflex; ECOG, Eastern Cooperative Oncology Group.
Psychometric Analysis

Psychometric analyses measure overall neurologic dysfunction and have been used to assess neurologic dysfunctions, including diabetic PN. The Semmes-Weinstein monofilament test measures the touch sensation on extremities with monofilaments. The Jebsen Test of Hand Function assesses daily activities requiring use of hands, such as writing. The Grooved Pegboard Test measures hand-eye coordination by assessing how efficiently patients handle grooved pegs. We evaluated the ability of these psychometric tests to predict MTSA-induced PN in the NCI ixabepilone phase II clinical trial of 47 patients with breast cancer. Our preliminary analyses indicated that results from psychometric tests, especially the Jebsen Test of Hand Function and Grooved Pegboard Test, have significant utility for prediction of development of ixabepilone-induced PN. Because these tests have not been evaluated in chemotherapy-induced PN, they need to be validated in a large prospective trial.

Electrophysiologic Testing

Nerve conduction study (NCS) and needle electromyography (EMG) are also used to objectively assess PN. Axonal neuropathy is identified by NCS as a low compound muscle action potential and by needle EMG as fibrillation; pure demyelinating neuropathy is identified by NCS as slow conduction velocity and prolonged distal latencies and by needle EMG as fibrillation; pure demyelinating neuropathy is identified by NCS as slow conduction velocity and prolonged distal latencies and by needle EMG as positive sharp wave activity. In paclitaxel-induced neuropathy, both axonal degeneration and demyelination patterns are possible on NCS, and frequently, sensory nerve potentials of the sural nerve are reduced or absent.

Management of MTSA-Induced Neuropathic Pain

No specific treatments for MTSA-induced PN are available. MTSA-induced PN generally improves when MTSA dose is reduced or MTSA therapy is delayed or completed. Approximately half of the patients with PN by polyoxyethylated castor oil–based paclitaxel experienced the improvement of PN within 9 months after cessation of paclitaxel treatment. Grade 3 or 4 PN induced by ABI-007 improved in a median 22 days after interruption of treatment. The median interval to improvement of grade = 2 PN induced by ixabepilone was 46 days for the every-3-week schedule and 15 days for the daily × 5 every-3-week schedule.

Neuroprotective Agents

Several types of neuroprotective agents have been tested for MTSA-induced neuropathy in animal models and clinical trials. Agents evaluated for potential neuroprotective effect in taxane-based chemotherapy are listed in Table 5.
Recombinant human leukemia inhibitory factor (ie, AM424) is a cytokine with neuroprotective effects that induces gene expression, proliferation, and regeneration of neurons. In a randomized, double-blind, placebo-controlled phase II trial of 117 patients with solid tumors who were treated with combination chemotherapy of carboplatin and paclitaxel (175 mg/m²), AM424 did not prevent significant PN as measured by standardized composite peripheral-nerve electrophysiology and by the vibration perception threshold.

Amifostine. Amifostine is an inorganic thiophosphate, a prodrug of free thiol (WR-2721), that may act as a scavenger of free radicals. In a randomized, nonblinded, phase II study of paclitaxel (250 mg/m² every 3 weeks) in breast cancer, there was no significant difference in neurotoxicity between patients receiving (n = 20) or not receiving (n = 20) amifostine (910 mg/m²). Although there are several randomized trials studying the neuroprotective effect of amifostine in patients receiving paclitaxel and carboplatin, the neuroprotective effect of amifostine has not been proven because of conflicting study results. The 2002 American Society of Clinical Oncology practice guideline stated that “there are no data to support the use of amifostine for prevention of paclitaxel-associated neurotoxicity.”

**Table 5. Agents That Have Been Evaluated for Potential Neuroprotective Activity in Taxane-Based Chemotherapy**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Clinical Trial</th>
<th>Reference</th>
<th>No. of Patients</th>
<th>Chemotherapy Used in the Trial</th>
<th>Overview of Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amifostine</td>
<td>Double-blind, placebo-controlled, randomized phase II</td>
<td>Hilpert et al</td>
<td>72</td>
<td>Paclitaxel/carboplatin</td>
<td>Significant improvement of sensory neuropathy in objective neurologic assessment but no difference in self-assessed symptoms</td>
</tr>
<tr>
<td></td>
<td>Randomized phase II</td>
<td>De Vos et al</td>
<td>90</td>
<td>Paclitaxel/carboplatin</td>
<td>Significantly decreased incidence of grade 2 sensory neuropathy</td>
</tr>
<tr>
<td></td>
<td>Randomized phase III</td>
<td>Lorusso et al</td>
<td>187</td>
<td>Paclitaxel/carboplatin</td>
<td>Significant reduction of grade 3 or 4 neuropathy</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>Moore et al</td>
<td>27</td>
<td>Paclitaxel/cisplatin</td>
<td>No significant difference</td>
</tr>
<tr>
<td></td>
<td>Randomized phase III</td>
<td>Seveida et al</td>
<td>89</td>
<td>Paclitaxel/carboplatin</td>
<td>No significant difference</td>
</tr>
<tr>
<td></td>
<td>Double-blind, placebo-controlled phase III</td>
<td>Leong et al</td>
<td>60</td>
<td>Paclitaxel/carboplatin/radiation</td>
<td>No significant difference</td>
</tr>
<tr>
<td></td>
<td>Randomized phase II</td>
<td>Gelmon et al</td>
<td>40</td>
<td>Paclitaxel</td>
<td>No significant difference</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>Socinski et al</td>
<td>21</td>
<td>Paclitaxel/carboplatin</td>
<td>No significant difference</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>Robinson et al</td>
<td>16</td>
<td>Paclitaxel</td>
<td>No significant difference</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>National Institutes of Health</td>
<td></td>
<td>Treatment of paclitaxel-induced neuropathy</td>
<td>Ongoing</td>
</tr>
<tr>
<td>BNP7787</td>
<td>Phase I</td>
<td>Takeda et al</td>
<td>22</td>
<td>Paclitaxel/cisplatin</td>
<td>Decreased incidence of grade 2 or higher neuropathy</td>
</tr>
<tr>
<td></td>
<td>Phase III</td>
<td>National Institutes of Health</td>
<td></td>
<td>Paclitaxel</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Dimesna</td>
<td>Randomized phase II</td>
<td>National Institutes of Health</td>
<td></td>
<td>Docetaxel/cisplatin</td>
<td>Ongoing</td>
</tr>
<tr>
<td>AM424 (rhuLIF)</td>
<td>Randomized, double-blind, placebo-controlled phase II</td>
<td>Davis et al</td>
<td>117</td>
<td>Paclitaxel/carboplatin</td>
<td>No significant difference</td>
</tr>
<tr>
<td>Acetyl-l-carnitine</td>
<td>Phase II</td>
<td>Bianchi et al</td>
<td>25</td>
<td>Paclitaxel or cisplatin</td>
<td>Improved sensory and motor neuropathy grade</td>
</tr>
<tr>
<td></td>
<td>Pilot study</td>
<td>Maestri et al</td>
<td>27</td>
<td>Paclitaxel and/or cisplatin</td>
<td>Improvement of peripheral neuropathy in 73% of patients</td>
</tr>
<tr>
<td>Glutamine</td>
<td>Phase II</td>
<td>Stubblefield et al</td>
<td>48</td>
<td>Paclitaxel</td>
<td>Significantly less weakness, less loss of vibratory sensation, and less toe numbness than controls</td>
</tr>
<tr>
<td></td>
<td>Placebo-controlled, double-blind, randomized crossover trial</td>
<td>Jacobson et al</td>
<td>36</td>
<td>Paclitaxel</td>
<td>No significant difference</td>
</tr>
<tr>
<td></td>
<td>Phase II</td>
<td>Vahdat et al</td>
<td>45</td>
<td>Paclitaxel</td>
<td>Significant reduction in the severity of peripheral neuropathy</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Randomized</td>
<td>Argyriou et al</td>
<td>31</td>
<td>Paclitaxel and/or cisplatin</td>
<td>Reduced incidence of neurotoxicity</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Randomized, placebo-controlled, double-blind phase III</td>
<td>National Institutes of Health</td>
<td></td>
<td>Paclitaxel or other neurotoxic chemotherapy</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
The efficacy of neuroprotective agents needs to be validated in well-designed, randomized, placebo-controlled trials. Currently, lamotrigine (NCCTG-N01C3), amifostine (NCT00078845), dimesna (CALGB-30303), and BNPP7787 (DM30203R) are being evaluated in phase II or III clinical trials of MTSA-containing chemotherapy regimens for the prevention of chemotherapy-induced neuropathy.110,113,119,131

Current Approach to the Management of MTSA-Induced Neuropathy

Early detection of PN during MTSA-based chemotherapy is critical to prevent progression to grade 3 or 4 PN. If grade ≥ 2 PN is diagnosed, it is prudent to hold MTSA until PN improves to at least grade 1, and then resume MTSA at a reduced dose. At present, there is no test that can be recommended to predict PN, but future clinical trials with tests discussed in this review are critical to advance the field. Gabapentin has been shown to provide relief of symptoms such as tingling or neuropathic pain and can be recommended.

FUTURE DIRECTIONS

Because understanding the exact mechanism of MTSA-induced neuropathy is essential for its management and prevention, reliable in vitro and animal models of MTSA-induced neuropathy should be developed. Current neuropathy grading systems should be consolidated into a reliable system so that neurotoxicity data from different clinical trials can be objectively compared. The reporting systems of clinical trials need to be standardized to collect more accurate data regarding MTSA-induced PN such as onset and duration of PN and cumulative dose. New measures for noninvasive evaluation of MTSA-induced neuropathy are needed to decrease interobserver and intraobserver variation in assessing MTSA-induced neuropathy. Finally, effective neuroprotective agents should be developed to prevent MTSA-induced neuropathy.

REFERENCES

11. Seidman AD, Berry D, Cirincione C, et al: CALGB 9840: Phase III study of weekly (W) paclitaxel (P) via 1-hour infusions versus standard (S) 3-hour infusions every third week in the treatment of metastatic breast cancer (MBC), with trastuzumab (T) for HER2 positive MBC and randomized for T in HER2 normal MBC. J Clin Oncol 22:6s, 2004 (suppl 14; abstr 512)
15. Mouridsen H, Harvey V, Semiglazov V, et al: Phase III study of docetaxel 100 versus 75 versus 60 mg/m² as second line chemotherapy in advanced breast cancer. 25th Annual San Antonio Breast Cancer Symposium, San Antonio, TX, December 11-14, 2002 (abstr 327)

10.4161/cno.1639


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93. Trites R: Neuropsychological Test Manual. Ottawa, Ontario, Canada, Royal Ottawa Hospital, 1977
113. National Institutes of Health: Docetaxel and cisplatin with or without dexamethas in treating patients with stage IIIB or stage IV non-small cell lung cancer. http://clinicaltrials.gov/ct/show/NCT00077311
120. Santini V: Amifostine: Chemotherapeutic and radiotherapeutic protective effects. Expert Opin Pharmacother 2:479-489, 2001


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Author Contributions

Conception and design: James J. Lee, Sandra M. Swain
Provision of study materials or patients: James J. Lee, Sandra M. Swain
Collection and assembly of data: James J. Lee, Sandra M. Swain
Data analysis and interpretation: James J. Lee, Sandra M. Swain
Manuscript writing: James J. Lee, Sandra M. Swain
Final approval of manuscript: James J. Lee, Sandra M. Swain