dividing patients into luminal A/luminal B/HER2 positive/basal-like subtypes by gene signature or by IHC4 immunohistochemical subtype.⁵ The Southwest Oncology Group (SWOG) S0221 trial, presented at the 2013 Annual Meeting of the American Society of Clinical Oncology,⁶ redefined “optimal” dose-dense paclitaxel and demonstrated that low-dose weekly paclitaxel has fewer adverse effects than the standard biweekly schedule for patients with early-stage breast cancer. One of the messages from this study is that weekly paclitaxel therapy obviates the need for granulocyte colony-stimulating factor support and reduces neurotoxicity, even though the schedule remains “dose dense” compared with a standard every-3-weeks paclitaxel regimen. This is particularly important given the concern, expressed by many, of the economic impact of the overuse of dose-dense therapy in hormone-sensitive disease.⁷

We are gravely concerned that the widespread adoption of intensive chemotherapy for all patients with node-positive early breast cancer represents overtreatment of many and risks our reproducing mistakes of the past, when we believed that high-dose chemotherapy and transplantation would result in cure for metastatic breast cancer.

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Reply to E.J. Moylan et al

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-38 study was designed to determine whether gemcitabine (G) added to dose-dense paclitaxel (P) following dose-dense doxorubicin and cyclophosphamide (dose-dense AC followed by PG) would improve outcomes in women with node-positive breast cancer relative to both dose-dense AC followed by P and docetaxel (T) AC (TAC).¹ Dose-dense AC followed by P had been defined as an optimal adjuvant chemotherapy regimen with a toxicity profile that allowed for the addition of G and represented the conventional control arm for B-38. However, it was recognized that if dose-dense AC followed by PG improved outcomes over dose-dense AC followed by P, questions about the activity of the regimen relative to an optimal T-based regimen would persist, so B-38 included TAC as a second control arm. Inclusion of what were perceived as two optimal adjuvant chemotherapy regimens as controls also provided the opportunity for direct comparison of the two regimens in a large phase III trial.

Results showed no benefit with the addition of G and no statistical differences in efficacy between the control regimens. However, toxicity profiles differed; thus, physicians and patients can now choose an anthracycline and taxane regimen based on considerations of schedule and toxicity, not relative efficacy. As

Moylan et al² point out, there was no statistically significant difference between dose-dense therapy and TAC in the estrogen receptor (ER) –positive cohort, which supports our statement regarding these findings. The results from B-38 were analyzed and submitted for publication before results from the referenced Southwest Oncology Group (SWOG) study were reported. Clearly, the use of weekly paclitaxel is an acceptable alternative to the dose-dense schedule of four cycles of paclitaxel, but it may be associated with more neurotoxicity. The meta-analysis by Bonilla et al is not based on data from trials but from a literature review. In fact, the authors stated in the conclusion, “However, additional data from randomized controlled trials are needed before dose-dense therapy can be considered as the standard of care.”³ NSABP B-38 is one such trial, with almost 5,000 patients randomly assigned.

Moylan et al express “grave concerns” about the characterization in our study of the control regimens with equivalent efficacy as optimal, inferring that we were advocating for indiscriminant use of these regimens in all patients with node-positive, ER-positive breast cancer. This was clearly not the theme of our discussion. B-38 was designed in 2002, was activated in 2004, and completed accrual in 2007. Perou et al⁴ first described their intrinsic breast cancer types by unsupervised hierarchical clustering analysis in 2000. The apparent utility of the Oncotype DX recurrence score assay to identify subgroups of patients with ER-positive breast

cancer who did not derive benefit from chemotherapy was reported in 2006 by the NSABP in node-negative patients^{5,6} and by SWOG in 2009 in node-positive patients.⁷ As a result of these and other studies, it has been increasingly recognized that the degree of benefit a patient receives from chemotherapy depends on the molecular subtype of the tumor. As stated in our discussion, biology must be the most important consideration for the development of future trials. The era of large adjuvant trials that do not consider molecular subtypes has run its course.

We agree that many patients with node-positive, ER-positive breast cancer may not require a third-generation adjuvant regimen or need chemotherapy at all. Trials such as RxSPONDER (NCT01272037), which is evaluating the role of chemotherapy in node-positive patients with low Oncotype DX recurrence scores, are needed to determine whether promising predictive markers will be able to define groups of ER-positive patients who will not benefit from chemotherapy. Conversely, we should be recruiting patients with high-risk ER-positive tumors to trials such as SWOG 1207/NSABP B-53 (NCT01674140), which is evaluating the addition of a mammalian target of rapamycin inhibitor to endocrine therapy, rather than continuing to address nuances of chemotherapy.

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Guidelines for Long-Term Steroid Therapy in End-of-Life Palliative Care

TO THE EDITOR: We read the recent article by Yennurajalingam S. et al,¹ in which they described the effect of dexamethasone in reducing cancer-related fatigue, with great interest. Steroid therapy has been a mainstay of palliative care since the 1980s.^{2,3} Indications of short-term steroid therapy in oncological emergencies include bowel obstructions, spinal cord compression, and superior vena cava syndrome. In addition, steroids can be useful for the treatment of nausea, dyspnea, anorexia, weight loss, fatigue, and in improving a patient's general feeling of well-being. However, steroids have a limited effect (lasting for up to 4 weeks) on these symptoms.⁴ Although the benefits of steroids generally outweigh its risks during end-of-life palliative care, adverse events may still occur and are more likely to develop on administration of higher doses of steroid. Therefore, careful consideration is necessary before prescribing high doses of steroids.⁵ In addition, steroid therapies in cases of end-of-life palliative

care are usually either gradually tapered or steadily increased, without sufficient available data on the long-term effects.

We were convinced with the statement of Yennurajalingam S. et al,¹ which concluded that dexamethasone, at a dose of 8 mg per day, was more effective than placebo in reducing cancer-related fatigue in 2 weeks. Although the fact that the effect of dexamethasone could be measured only for 15 days was listed as a limitation in the study, life expectancy of 4 weeks or longer was one of the inclusion criteria. Thus, we would like to know how the patients were treated with dexamethasone beyond the 2-week time period. In other words, did they continue with the same dose of dexamethasone or was it tapered off or increased? In addition, we would like to know the adverse effects associated with continuing dexamethasone beyond 2 weeks. Finally, we agree with the authors that long-term studies to analyze the efficacy and safety of steroid therapy are needed, along with further clarification on how palliative steroid treatment should be continued in patients who require this therapy beyond 2 weeks.

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