staging system is ever ideal. Perhaps more robust data will be produced by a new international effort spearheaded by Lorch and Beyer, as mentioned in their letter. Our group, the Shamash group, and numerous other centers will contribute patient data.

Kondagunta et al. address other salvage chemotherapy strategies. They imply that paclitaxel should be an integral part of treatment regimens. Unfortunately, there are no data to substantiate or refute this claim. Motzer et al. reported data on 37 previously treated patients with unfavorable prognostic features who received two cycles of paclitaxel plus ifosfamide followed by three cycles of high-dose carboplatin plus etoposide given 14 to 21 days apart. Of these 37 patients, 15 (41%) had durable remissions with a median follow-up of 30 months. A follow-up report assessed an additional 48 patients, and 24 of the 48 remained progression-free with a median follow-up of 40 months. In our study, 67 of 123 similar patients (54.5%) had a durable remission with a median follow-up of 48 months. Thus, there is no clear indication that paclitaxel, dose-dense therapy, or a third course of high-dose carboplatin plus etoposide is required.

Kondagunta and colleagues also question whether high-dose salvage chemotherapy is required for patients with a low risk of relapse. In the study by Kondagunta et al., 29 of 43 patients had a durable remission with four courses of standard-dose paclitaxel plus ifosfamide plus cisplatin. By contrast, in our study, 49 of 61 similar patients with low-risk disease had a durable remission. I agree with Kondagunta and colleagues that only a phase 3 trial can prove the superiority of treatment in these patients with low-risk disease. However, it is unknown whether four courses of paclitaxel (250 mg per square meter of body-surface area, given as a 24-hour continuous infusion) plus ifosfamide (1.2 g per square meter for 5 days) plus cisplatin (20 mg per square meter for 5 days) are less toxic than our tandem transplantation regimen. Treatment-related mortality was similar (2%), neutropenic fever resulted in 26 hospitalizations for 22 patients (48%), and 3 patients (7%) had grade 4 or 5 renal toxic effects.

De Giorgi et al. mention the less favorable results achieved when only a single course of high-dose therapy was used, providing further support for the value of a tandem transplantation regimen.

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Rosiglitazone and the FDA

TO THE EDITOR: In his Perspective article (Aug. 30 issue), Dr. Rosen discusses the recent Food and Drug Administration (FDA) advisory committee meeting on rosiglitazone. He also calls for approval of antidiabetic drugs based on long-term clinical outcomes, not on the surrogate of glycated hemoglobin, a measure of glycemic control. Although he does not describe a specific study, we assume he is suggesting that approval should require evidence that cardiovascular events, a major long-term complication of diabetes mellitus, are reduced. This change could have major implications for the availability of treatments for type 2 diabetes.

All drugs currently approved for the treatment of diabetes are indicated to improve glycemic control. Reductions in glycated hemoglobin levels directly reflect improved glycemic control, leading to a lessening of hyperglycemic symptoms, including polydipsia, polyuria, and blurred vision. In this respect, the FDA views a reduction in the level of glycated hemoglobin as a well-validated surrogate for a beneficial effect on the immediate clinical consequences of diabetes.

There are reasonably strong data supporting a reduced risk of microvascular complications with improved long-term glycemic control, although not for most individual drugs, and no drug carries a claim for such an effect. Clear evidence of a reduced risk of macrovascular complications in type 2 diabetes associated with any antidiabetic agent has yet to be established. Because patients with type 2 diabetes have progressive worsening of glycemic control over time, long-term trials will probably need to compare one drug within a multidrug regimen with other available therapies, making demonstration of the effect of any single drug a formidable task.

A proposal to base future approvals on evidence of long-term cardiovascular benefit would significantly delay the availability of new drugs for the treatment of diabetes and might make development of new drugs impossible. One would also need to question why existing therapies, all lacking such evidence of benefit, should persist. This concern does not minimize the importance of determining whether the treatment of diabetes with antidiabetic drugs reduces long-term cardiovascular complications. Such an effect is, after all, one of the major intents of the treatment of diabetes.

A separate issue raised in the case of rosiglitazone, but one that is not limited to treatments for diabetes, is whether a drug might have adverse cardiovascular effects. For rosiglitazone, the recommendations of the advisory committee are currently under consideration by the FDA. The FDA considers cardiovascular safety matters during premarketing review and postmarketing activities, particularly when there is a safety signal that raises a concern. For this very reason, we recently requested a phase 3 clinical outcome trial of an investigational antidiabetic drug on the basis of