Procarbazine and Infertility in Low-Grade Gliomas in Children

To the Editor: We read with interest the publication by Ater et al1 on the comparison between two different chemotherapy regimens for low-grade glioma in children. The primary aim was to compare the event-free survival but the stated secondary aims included a comparison of toxicity of the two regimens. The discussion mentions the fear that the TPCV (thioguanine, procarbazine, CCNU, vincristine) regimen may increase the risk of secondary neoplasms however there is no mention of the risk of infertility from procarbazine in TPCV. The protocol includes procarbazine 200 mg/m²/cycle for a total of eight cycles giving a cumulative dose of 1,600 mg/m². The TPCV protocol was based on the TPDCV (thioguanine, procarbazine, dibromodulcitol, CCNU, vincristine) regimen with the exclusion of the dibromodulcitol but even a recent publication2 on 15 years follow-up of pediatric patients with low-grade hypothalamic/chiasmatic glioma treated with this regimen makes no mention of fertility or follicle-stimulating hormone measurements. It is well known from the literature on Hodgkin lymphoma in children that there is a relationship between the cumulative doses of gonadotoxic drugs, especially procarbazine, and the extent of testicular damage and the azoo/hypospermia is usually irreversible.3,4 With an overall survival for low-grade gliomas of 85% and the likelihood that the majority of these patients will reach adulthood, lasting testicular damage with severely impaired spermatogenesis could be particularly distressing to the many young adults cured of their glioma. In addition, the vast majority of these patients will be too young for fertility preservation techniques such as sperm banking. This issue needs to be addressed in the decision making process regarding treatment options together with the family of a child with a low-grade glioma and should be documented in long-term follow-up studies of TPCV and similar procarbazine-containing regimens. Considering the morbidity of gonadal dysfunction, efforts are needed to test alternative treatment regimens with less gonadotoxic chemotherapeutic agents or hopefully new biologic targeted therapies for low-grade gliomas in children.

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Authors’ Disclosures of Potential Conflicts of Interest
The author(s) indicated no potential conflicts of interest.

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DOI: 10.1200/JCO.2012.44.9462; published online ahead of print at www.jco.org on November 13, 2012

Reply to H. Toledano et al

The letter by Toledano et al2 raises a concern about procarbazine and infertility that warrants discussion. In our article reporting the initial results of treatment of young children with two regimens of chemotherapy for progressive low-grade gliomas, the risk of second neoplasms is reported and discussed, because this is one of the primary end points of this study.2 The primary end points were tumor progression, death, or second neoplasm. Many of the other secondary outcomes that are also important, such as endocrine and intellectual function, will be reported separately. These long-term issues were beyond the scope and space limitation of this initial paper.

The literature in Hodgkin lymphoma is extensive, and as Toledano et al2 point out, the risk of infertility has been associated with cumulative doses of alkylators and possibly procarbazine. While the brain tumor population is different from the Hodgkin lymphoma population, it is helpful to put these Hodgkin regimens and total cumulative doses into perspective. The two articles referenced in the letter3,4 both included regimens with higher cumulative doses of procarbazine that utilized in the TPCH (thioguanine, procarbazine, lomustine, and vincristine) regimen reported in this article, which has a total cumulative dose 1.6 g/m² for the entire treatment. In the Hobbie et al3 paper, nine of 11 males were infertile by semen analysis. However, all but one of these boys received over 2.8 g/m² of procarbazine, some as high as 4.2 to 8.4 g/m². In addition, a recent paper reported survival and fertility results with a tailored BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone) regimen. With a minimum of six cycles of standard BEACOPP (total cumulative dose of procarbazine = 4.2 g/m²), the fertility was preserved in 94% of the young women in this study.4

The majority of the children treated on this protocol had tumors in the central part of the brain, where curative surgery was not possible. The presence of a tumor in the hypothalamic/thalamic region has risk of endocrine deficits and potential infertility due to the surgery, tumor itself, and the use of cranial radiation5,6 so baseline and follow-up endocrine evaluations were required on this study. However, even when the endocrine results are available, the issue of the role...