Response:

Mortality in adults with ITP

We thank Drs Djulbegovic and Cohen for their comments on our recently published study.1 As they pointed out, we estimated the rate of fatal hemorrhage for patients with refractory idiopathic thrombocytopenic purpura (ITP) at 0.019 cases per patient-year at risk (where time at risk was defined as time with fewer than 30×10⁹/L platelets), using a method previously described by Cohen et al.2 Unfortunately, Drs Djulbegovic and Cohen erroneously assumed that nonhemorrhagic deaths were included in the death rate of 0.019. But this rate only represents fatal hemorrhages and is entirely in accordance with their original estimates obtained from pooled information from 17 case series.

Here we want to address 2 other important issues: First, nonhemorrhagic deaths should also be defined when defining to what extent ITP compromises life expectancy. This led us to suggest that the only reliable estimate of the risk to die from ITP is obtained by comparing the mortality risk of patients with ITP with mortality risks in the general population, the method applied in our study. Second, hemorrhagic and nonhemorrhagic deaths should be differentiated. In our population, deaths due to lethal infections exceeded deaths due to bleeding, necessitating a discussion about the severe adverse effects of presently available treatment options for refractory ITP.

Therefore, although we did not advocate a “watchful waiting strategy,” our results underscore the fact that risks of hemorrhages and the risks of serious adverse effects must be carefully weighed when administering second-line treatment for refractory ITP.

Johanna E. A. Portielje, Rudi G. J. Westendorp, Hanneke C. Kluin-Nelemans, and Anneke Brand

Correspondence: Johanna E. A. Portielje, Department Medical Oncology, Daniel den Hoed Kliniek, Rotterdam Cancer Institute, Groene Hilledijk 301, Rotterdam 3075 EA, The Netherlands; e-mail: portielje@oncol.azr.nl

References

To the editor:

Attribution of posttransplantation toxicity to methotrexate regarding genotype of methylenetetrahydrofolate reductase gene (MTHFR) polymorphism needs further clarification

Ulrich et al recently reported the association between a polymorphism of folate-metabolizing enzyme, methylenetetrahydrofolate reductase gene (MTHFR), 677C>T and risk of posttransplantation complications.3 The authors showed the significantly reduced oral mucositis index scores,4 and not significant but delayed hemolologic recovery among patients with the TT genotype, compared with those with the CC genotype. They hypothesized that a modification of toxicity by MTHFR genotype was due to methotrexate (MTX) use for posttransplantation prophylaxis for graft-versus-host disease (GVHD) because MTX is the antifolate drug whose common toxicity includes oral mucositis and hematologic complications.3 Previously, a similar finding that the grade 4 neutropenia (NCI-CTC criteria) following MTX including adjuvant-combined chemotherapy for breast cancer is more frequently observed among TT genotype was reported by Toffoli et al.5 Although we basically agree with the concept that genetic variation of MTHFR may predispose certain kinds of clinical/prerclinical status as we have already reported,5 we are hesitant to view MTX as a modifier of the causal association between the genotype and toxicity.

In general, oral mucositis may occur in the conditioning regimens applied in their study even if they do not include MTX. As Ulrich et al mentioned, the most important point is the imbalances in folate pools in those with the TT genotype, which results in the decreased availability of folate for recovery by DNA synthesis. This means the MTHFR genotype represents a lesser ability to recover from the chemotherapy, not only by means of MTX. Their study did not examine the difference in toxicity for patients treated with MTX compared with those treated without MTX. In addition, no information on other important factors regarding oral mucositis, such as the pretransplantation condition of the oral cavity or HLA-matching status, was provided in this study. Because oral mucositis has been recognized as one of the prognostic factors for hematopoietic cell transplantation,4 a study exploring the predisposing factors would be important for clinical situations. We believe that these factors should be taken into account before drawing final conclusions and starting a dose-adjustment study of MTX for GVHD prophylaxis.

Keltaro Matsuo, Ritsuro Suzuki, Yasuo Morishima, and Nobuyuki Hamajima

Correspondence: Keltaro Matsuo, Aichi Cancer Center Research Institute, Division of Epidemiology and Prevention, 1-1 Kanokoden Chikusa-ku Nagoya 464-8691, Japan; e-mail:kmatsuo@achc.gov.aichi.cc.pref.aichi.jp

References
Response:

*MTHFR* polymorphism, DNA repair capacity, and methotrexate toxicity

Matsuo et al raise the question of whether the *MTHFR* 677C>T polymorphism may affect oral mucositis in marrow-transplantation patients, independent of treatment with the antifolate drug methotrexate (MTX). The mechanism we proposed for explaining our findings involves (a) decreased provision of folate for nucleotide synthesis among patients with lower *MTHFR* activity (TT genotype), (b) a decreased ability for DNA repair, and therefore (c) greater damage and delayed healing of the oral mucosa among these patients. Naturally, one can expect similar effects in any situation involving the need for DNA repair. As we discussed, the conditioning regimens used in marrow-transplantation patients (cyclophosphamide / total body irradiation [Cy/TBI] or busulfan/cyclophosphamide [Bu/Cy]) by themselves induce oral mucositis.

But while the conditioning regimens result in oral mucositis, MTX has “additive” effects: when administered after transplantation for acute graft-versus-host disease (GVHD) prophylaxis, it can substantially increase the level of mucosal damage and delay healing. We have shown that, among marrow-transplant patients with Cy/TBI or Bu/Cy conditioning, MTX administration results in 45% of patients experiencing severe oral mucositis, compared with 8% of patients without MTX. Others have reported similar results.

Thus a substantial amount of oral mucositis in the transplantation setting can be attributed to MTX administration, and an effect of the *MTHFR* polymorphism can be more easily observed in this situation of extreme folate depletion. One may expect a close link between a polymorphism affecting the balance of folate metabolites and the effect of an antifolate drug.

Our group, as well as others, has shown that the risk of colorectal neoplasia associated with the *MTHFR* polymorphism varies by folate status, with an increased risk observed only among individuals with low folate intake or biomarkers indicating low folate status. Our findings on MTX toxicity, which induces a folate-depleted state, are consistent with this model of gene-nutrient interaction.

Matsuo et al were further concerned that information on the pretransplantation condition of the oral cavity or HLA-matching status was not considered. HLA-matching status was in our population equivalent to the type of conditioning regimen and was adjusted for in the statistical analyses. Oral mucositis scores before transplantation were extremely low (usually 0-1) and did not affect our results. Nevertheless, we agree with Matsuo et al that our findings need to be replicated in other populations, and the occurrence of GVHD needs to be evaluated before dose adjustment of MTX should be considered.

Cornelia M. Ulrich, Rainer Storb, Mark M. Schubert, and John D. Potter

Correspondence: Cornelia M. Ulrich, Fred Hutchinson Cancer Research Center, Cancer Prevention Research Program, 1100 Fairview Ave N, MP-900, Seattle, WA 98105-1024; e-mail: nulrich@fhcrc.org

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Keitaro Matsuo, Ritsuro Suzuki, Yasuo Morishima and Nobuyuki Hamajima