The natural history of refractory idiopathic thrombocytopenic purpura

Portielje et al\(^1\) recently reported a study on the natural history of idiopathic thrombocytopenic purpura (ITP). Although the design of their study still falls short of a “gold-standard” inception cohort, prospective study required to reliably assess the natural history of a disease,\(^2\) their study represents the best available to date to assess the prognosis of adult patients with ITP. The study reaffirmed previous analysis of data that patients with mild and moderate thrombocytopenia have a benign course.\(^3\) Portielje et al\(^1\) now show that these patients do not have their life expectancy (LE) compromised. But they also show that patients with refractory ITP with persistently low platelet counts (below 30 000/μL) have 4.2-fold increased mortality risk in comparison with the general population. In this population the authors calculated the death rate of 0.019 cases per patient-year at risk. They compared this estimate with our estimate of the fatal bleeding rate in patients with refractory ITP of 0.0162 to 0.0389 cases per patient-year at risk.\(^4\) Our estimate, based on pooled data available in literature up to year 1998, showed a considerable compromise in LE in patients with refractory, untreated ITP.\(^5\) But by analyzing the cause of death, Portielje et al pointed out that half of the deaths were due not to bleeding but rather to the lethal infections likely related to the treatment.

To investigate whether this suggested estimate of the fatal bleeding rate would change calculation of LE in refractory ITP, we assumed that the bleeding rate in refractory, untreated patients would amount to half of the death rate calculated by Portielje et al (= 0.019/2). Even with this new assumption, our model\(^4\) again demonstrates that LE and QALE (quality-adjusted life expectancy) in patients with refractory ITP are severely compromised (Figure 1). For a typical 30-year-old female, LE is decreased by 10.43 years (an average LE for a 30-year-old healthy female is 49.57 years and an average LE for a 30-year-old female with refractory ITP calculated in our model is 39.14 years) and by 8.72 of QALE (36.21-27.49). This result is based on the constant bleeding risk. We also analyzed the model assuming age-dependent bleeding risk (as was done in our original model). Unfortunately, Portielje et al did not provide death-rate calculations according to age. But since their estimate was quite close to ours (see above), we reid the analysis by assuming half of the fatal-bleeding age-adjusted risk in our original model. As expected, under these assumptions LE and QALE do not change significantly from the model based on the constant bleeding risk for younger patients but are significantly affected for older patients. For example, under the constant-bleeding risk model (Figure 1), a 60-year-old female with untreated refractory ITP will have LE decreased by 2.6 years compared with a healthy 60-year-old female. Under the age-adjusted risk model, a 60-year-old female would have LE decreased by almost 10 years (results not shown).

In conclusion, the best data so far indicate that patients with refractory, untreated ITP have a poor prognosis. If we are to believe the current data, then it is difficult to justify complacency in terms of a watchful waiting strategy. A separate issue is whether current available treatments do more good than harm, which neither our model nor Portielje et al’s study was designed to answer. As we noted,\(^4\) the only way to settle the issue of prognosis is to perform a well-designed prospective inception cohort study of patients with refractory ITP. Until that study is done, recommendations that patients with refractory ITP and low counts should be merely observed is difficult to justify.

References

Response:

Mortality in adults with ITP

We thank Drs Djulbegovic and Cohen for their comments on our recently published study. As they point 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 $3 \times 10^9$/L platelets), using a method previously described by Cohen et al. 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 addressed when defining to what extent ITP compromises life expectancy. This led us to suggest that the only reliable estimate of the risk of death 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. The authors showed the significantly reduced oral mucositis index scores, and not significant but delayed hematologic 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. 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. Although we basically agree with the concept that genetic variation of MTHFR may predispose certain kinds of clinical/preclinical status as we have already reported, 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, 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 464-8681, Japan; e-mail:k.matsuo@aichigw.aichi-cc.pref.aichi.jp

References

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Benjamin Djulbegovic and Yael Cohen