The Bleeding Risk and Natural History of Idiopathic Thrombocytopenic Purpura in Patients With Persistent Low Platelet Counts

Yael C. Cohen, MD; Benjamin Djulbegovic, MD; Orna Shamai-Lubovitz, MD; Benjamin Mozes, MD

Background: No firm data are available on the natural history of idiopathic thrombocytopenic purpura (ITP) or on mortality rates or frequency of major bleeding episodes associated with this condition. The disease is thought to have a relatively benign course, despite the frequent occurrence of very low platelet counts. This prevailing conception often guides therapeutic decisions.

Objective: To estimate the bleeding risk of ITP involving persistent low platelet counts (<30 x 10⁹/L) and its impact on prognosis.

Design: Age-adjusted bleeding risk was derived from a pooled analysis of ITP clinical series based on a systematic literature search. The risk estimate was incorporated into a Markov model to determine its impact on prognosis.

Results: Seventeen case series complied with inclusion criteria, including 1817 patients with ITP. There were 49 cases of fatal hemorrhage over an estimated 1258 to 3023 patient-years at risk. The rate of fatal hemorrhage before age adjustment was estimated at between 0.0162 and 0.0389 cases per patient-year. Age-adjusted rates were 0.004, 0.012, and 0.130 cases per patient-year for age groups younger than 40, 40 to 60, and older than 60 years, respectively. Predicted 5-year mortality rates ranged from 2.2% for patients younger than 40 years to 47.8% for those older than 60 years. A 30-year-old woman remaining thrombocytopenic due to ITP was predicted to lose 20.4 years (14.9 quality-adjusted life years) of her potential life expectancy. At age 70, predicted loss was 9.4 years (5.0 quality-adjusted life years).

Conclusions: Idiopathic thrombocytopenic purpura with persistent low platelet counts carries a grave prognosis. Therefore, an active therapeutic approach in the clinical management of affected patients should be considered. In view of the significant potential implications of the model results, we call for initiating a well-designed prospective inception cohort study of patients with ITP.

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PATIENTS AND METHODS

DERIVATION OF BLEEDING RISks

We considered patients with ITP to be at risk for major hemorrhage when their platelet counts fell below 30 × 10⁹/L. The analysis referred to 4 bleeding categories: (1) fatal bleeding events; (2) hemorrhagic strokes with residual disability; (3) major “transient” bleeding events requiring hospitalization, but without long-term sequelae (eg, upper gastrointestinal tract bleeding); and (4) minor oozing and bruising (eg, gingival bleeding event). We assumed no difference in bleeding rates between the sexes.

SELECTION OF STUDIES FOR POOLED ANALYSIS

We used the results of the extensive systematic literature search performed by the ASH panel for establishing practice guidelines for ITP. This search was extended to include later publications (years 1995-1998) using a MEDLINE query (keyword: idiopathic thrombocytopenic purpura/ITP, all fields, and all subheadings, limited to articles in the English language, excluding letters and case reports). Candidate articles were systematically reviewed to assess their appropriateness for inclusion in this analysis according to the following criteria: (1) studies that observed cohorts of patients with ITP over a period of at least 1 year (either prospective or retrospective); (2) either the number of deaths due to hemorrhagic events or the absence of such fatalities within the study period was clearly reported; (3) the study period had been sufficiently characterized (either exact patient-years of observation reported or both maximum and median follow-up periods); and (4) the number of patients at risk for thrombocytopenic hemorrhage during the study follow-up period was reported (ie, patients with periods of platelet counts <30 × 10⁹/L).

CALCULATION OF THE RISK FOR MAJOR BLEEDING

The bleeding rate was calculated as the ratio between the pooled number of bleeding events and the pooled patient time at risk for major bleeding in the studies included in the analysis. The rates of fatal bleeding events and major nonfatal bleeding events were calculated separately. The calculation of the latter was based on the subset of articles that followed up and reported major, nonfatal bleeding events.

Patient time at risk for major bleeding events included the period prior to response to therapy in all patients and the follow-up period among refractory patients or patients who had experienced relapse. Time until response was estimated according to the treatment modality used: 2, 3, and 4 weeks for splenectomy, corticosteroid treatment, and cytotoxic therapy, respectively.

Of the 295 articles found in the ASH search and the 293 found in our MEDLINE extensions, 174-24 (Table 1) complied with our inclusion criteria. These studies included a total of 1817 patients with ITP. There were 49 cases of fatal hemorrhage. The total patient time at risk estimation of the follow-up period for patients who did not respond to therapy or those who experienced a relapse was either (1) the exact period of follow-up, when reported, or (2) when the exact period was not stated, we estimated a plausible range between a high boundary maximum follow-up period in the study and a low boundary (the median follow-up period). We selected this low boundary based on the assumption that patients who remained thrombocytopenic tended to continue with medical attention for longer rather than shorter periods. For patients who experienced relapse, time until relapse was subtracted from the follow-up period.

AGE ADJUSTMENT OF BLEEDING RISK

Age adjustment of bleeding risk was based on the findings of Cortelazzo et al, who reported the age-associated risk for major bleeding in chronic ITP. They reported an odds ratio (OR) of 2.8 for patients aged 40 to 60 years vs those younger than 40, and of 28.9 for those 60 years or older vs those younger than 40 years, for a major bleeding event due to ITP. Considering the low absolute annual fatal bleeding risk, these ORs were used as estimates of the relative risks. We performed a subanalysis of the articles that reported the age distribution of their populations. Assuming linear relations, a set of equations was derived based on the age distribution of the pooled cohort, the relative risks in different age groups, estimated patient time in each age group, and the total number of bleeding events. From these equations, the age-adjusted risks within each of the above age groups were determined (Appendix).

RISK FOR DISABLING HEMORRHAGIC STROKE

The incidence of disabling stroke was not specified in any of the studies included in our analysis. Since this complication has major long-term effects on QOL, we used an indirect approach to estimate its frequency, based on the outcomes of hemorrhagic stroke from all causes (ie, not necessarily related to ITP): (1) The proportion of strokes among patients with ITP and fatal bleeding events was calculated based on the studies in our analysis that reported the site of bleeding (ie, central nervous system, gastrointestinal tract, etc). (2) According to a recent quantitative epidemiological review of intracerebral hemorrhage (summarizing 4 outcome studies), the fatality rate was 30% to 50%, and the rate of long-term disability among survivors ranged from 13% to 46%. Accordingly, we assumed 40% mortality and 30% (among survivors) long-term disability among patients with ITP who experienced a hemorrhagic stroke. (3) Estimation of the incidence of nonfatal hemorrhagic strokes among patients with ITP was based on the assumption that the fatality rate of ITP-related hemorrhagic strokes is similar to that of hemorrhagic strokes not associated with ITP.

Continued on next page
The ratio of nonfatal to fatal strokes was estimated as 0.6: 0.4; therefore, the rate of nonfatal hemorrhagic stroke in ITP equals 0.6 × RFS/0.4, where RFS indicates the rate of fatal stroke in patients with ITP with persistent low platelet counts. The rate of disability among hemorrhagic stroke survivors was estimated as 30%; therefore, the rate of nonfatal hemorrhagic stroke in ITP equals (0.3 × 0.6 × RFS)/0.4, which equals 0.45 × RFS.

**MODELING THE NATURAL COURSE OF ITP**

A computerized Markov model was developed to simulate the course of a hypothetical cohort of patients with thrombocytopenia (platelet counts <30 × 10^9/L) due to untreated or refractory ITP (Figure 1). Initially, all cohort members are placed in the well-ITP state. At each cycle of the simulation (lasting 1 year), any cohort member may suffer a major hemorrhage that may be fatal, disabling, or transient. Accordingly, at the end of the cycle, members are transferred to dead or disabled states or remain in the well state. Major transient hemorrhagic events are assumed to exert a negative effect on ITP health states for 1 week. The probabilities of these events are determined according to the patient's age, based on the results of our pooled analysis. Patients also stand a chance of achieving a spontaneous remission, transferring into a remission state, or they may die from causes unrelated to ITP. The simulation continues until the entire hypothetical cohort has died. The QALE is calculated by summing up the number of patients in each state multiplied by the utility of that state, and dividing the sum by the cohort size. The average LE for cohort members is calculated similarly using a utility value of 0 for death and 1 year for all other states. The predicted LE and QALE of patients with ITP are compared with those of a healthy cohort of the same age (a model including only well and dead states).

The model was constructed using DATA 3.0 software (TreeAge Software Inc, Williamstown, Mass). Analyses of women aged 30, 50, and 70 years were affiliated with ages 30, 50, and 70 years in the model. Probabilities were based on the estimates from our pooled analysis.

The results of our pooled analysis are presented as base cases.

**PROBABILITIES AND UTILITIES**

**Major Bleeding Events**

Model probabilities were based on the estimates from our pooled analysis (Figure 2). Probabilities derived for age groups younger than 40, 40 to 60, and older than 60 years were affiliated with ages 30, 50, and 70 years, respectively. Linear interpolation was used to estimate bleeding probabilities for ages between these points.

**Spontaneous Remission**

Evidence is lacking for the rate of spontaneous remission, and although experts agree that this is infrequent, it was approximated to be 5% by the ASH panel. In the model, we assumed a probability of 0.1% per year throughout the patient's lifetime (5% over 50 years).

**Death Unrelated to ITP**

The model considered death from any reason other than ITP, according to age and sex. Probabilities were based on the report of the National Center for Health Statistics.

**Health State Utilities**

Utility coefficients introduced QOL weightings for the various health states into the model. Patients in remission were considered equivalent to the general population, based on a survey using the Quality of Well-Being Index (QWB). The QWB was previously used to estimate utility values for the general population, adjusted to age and sex. The QWB scale derives its values from an assessment of patient answers to questions directed toward current symptoms and health-related reductions in mobility and physical and social activity. Scale scores range from 0 (death) to 1.0 (asymptomatic functioning). Utility values for patients disabled by a hemorrhagic stroke were half of the utility value of healthy persons at the same age. Patients with thrombocytopenia but without major bleeding have some reduction in their well-being score because of restrictions of engaging in sport activities, tendency toward bruising and minor bleeding events, anxiety of potential hemorrhage, and the need for repeated blood withdrawal. For these patients, we used a utility value of 0.98 of their healthy counterparts, based on the analogous state of bleeding tendency from anticoagulant therapy. A utility value of 0 was used for a period of 1 week following events of major transient hemorrhage without long-term sequelae.

**SENSITIVITY ANALYSIS**

Sensitivity analysis was performed on all model estimates within plausible ranges within the DATA model. In addition, we used structural sensitivity analysis of assumptions regarding age adjustments. The model was modified to examine the effect of no age adjustment and different levels of relative risks among age groups. In addition, we examined the effect of using an analytic exponential equation based on the risk at 3 ages (30, 50, and 75 years) for calculation of age-adjusted risk.

**MODEL VALIDATION**

To validate the model’s predictions of survival unrelated to ITP, the probability of remission was set to 1.0 (bleeding rate drops to 0). The resulting LE was compared with those published by the National Center for Health Statistics.
per year for patients younger than 40 years and up to 13% per year for patients older than 60 years (Figure 3, left).

Estimation of the risk for major, nonfatal hemorrhage was based on 2 studies (with relatively elderly cohorts)\(^4,12\); 29 events were reported within an observation time ranging from 77 to 105 patient-years. Age-adjusted risk for an event of nonfatal major hemorrhage was found to be 3% (0.03) per year for patients younger than 40 years, and 71% (0.71) per year for patients older than 60 years (Figure 3, right).

Figure 4, top, shows the cumulative probability for fatal bleeding for periods between 6 months and 5 years for each of the age groups analyzed. Predicted 5-year fatality ranges from 2.2% for patients younger than 40 years to 47.8% for patients older than 60 years. Seventy-six percent of the patients older than 60 years who remain with persistent low platelet counts will undergo at least 1 major nonfatal bleeding event during 2 years of follow-up (Figure 4, bottom). A 30-year-old woman with low platelet counts stands a 16.3% chance of a fatal bleeding event (Figure 4, bottom). The rate is calculated as the ratio between the number of fatal bleeding events and the patient time at risk. Upper and lower limits of the intervals are based on the lower and upper estimates of patient-years of follow-up, respectively. The upper patient time estimate was based on the maximum follow-up time, the lower estimate, on the median follow-up time. The point estimate is the mean of the upper and lower estimates. (Intervals are missing in 2 studies: Guthrie et al\(^12\) reported exact patient time, and Rocco and Stein\(^21\) reported only the maximum estimate of follow-up time.) Studies in which the period was not specified have been ordered approximately, according to publication date.

**Figure 1.** The Markov model: a schematic illustration of the model, the Markov states (all capitals), and cycle transitions (initial-capped only). In a sample scenario, a patient starting off in the ITP (idiopathic thrombocytopenic purpura) state may die (of a bleeding event or an unrelated cause), transferring to the DEAD state; or may suffer a disabling stroke, transferring to the DISABLED state; or may achieve a remission, transferring to the REMISSION state. Otherwise, the patient will remain in the ITP state for the next cycle. (Transient events such as major bleeding events without long-term effects are not represented in this illustration.)

**Figure 2.** Pooled analysis of the annual rate of fatal hemorrhage among patients with persistent low platelet counts (<30 × 10^9/L). The rate is calculated as the ratio between the number of fatal bleeding events and the patient time at risk. (Nonconsecutive Series)
QUALITY OF THE DATA

Selection of studies for inclusion in the pooled analysis was based on a systematic and extensive search using explicitly defined inclusion criteria. Since no well-designed studies on the natural history of ITP with low platelet counts were found in the medical literature, we resorted to pooling data from uncontrolled, mostly retrospective clinical series—a relatively weak form of clinical evidence (only 2 prospective series were found22,23). Nevertheless, several indications support acceptability of the evidence from these series. All series used strict criteria for diagnosis of ITP; 16 of the 17 series stated the criteria explicitly (ie, low platelet count, megacaryocytosis on bone marrow, absence of splenomegaly, and ruling out other causes, including drugs, autoimmune diseases, infection, etc).

The use of retrospective series gives rise to concern of selection bias, ie, that the series include a high proportion of patients with ITP who are at increased risk. Some reassurance against this possibility is provided by the relative uniformity observed between the study estimates. Except for 1 outlier (a study of ITP in the elderly), the estimates of 16 individual trials from different settings were closely clustered around the pooled estimate (Figure 2). In addition, a subanalysis of 8 of the series, which included consecutive patients with ITP admitted to a health care center (either all patients with ITP or all those referred for splenectomy; Figure 2), revealed no difference in the resulting bleeding risk compared with the nonconsecutive series.

Another potential concern is that some of the series are relatively old (from the 1960s and 1970s), suggesting poorer prognosis compared with that of patients undergoing current treatment owing to less advanced medical care. Yet, as shown in Figure 2 in which the series are ordered chronologically, no such trend was observed. While these observations do not guarantee that the pooled estimates from these series would be equivalent to prospectively designed studies, we believe that they provide valuable reassurance supporting the accuracy of these estimates.

ANALYTICAL METHODS

We used data pooling and Markov modeling to estimate bleeding risk and its implications on patient prognosis, respectively. By applying these analytical methods we were able to model the natural course of ITP in patients with persistently low platelet counts.

Discrimination of High-Risk Subgroups

These methods enabled us to discriminatively simulate the health life course of a specific group of patients with ITP, ie, those patients among the series who remain with low platelet counts. We were also able to adjust for the increased risk at advanced age. This focus on high-risk patients is important because the ITP population is quite heterogeneous. It includes patients whose thrombocytopenia is not within severe levels (ie, >30 × 10^9/L), those who responded favorably to treatment, and those whose follow-up period did not extend through advanced age. Thus, the prognosis of an “average” patient with ITP would seem to be only mildly affected. This might ex-

**Table 1. Pooled Analysis of Bleeding Risk Among Patients With Idiopathic Thrombocytopenic Purpura and Low Platelet Counts**

<table>
<thead>
<tr>
<th>Reference</th>
<th>No. of Subjects</th>
<th>Age Groups, y</th>
<th>No. of Fatal Bleeding Events</th>
<th>Source of Bleeding Event</th>
<th>Patient-Year Estimates</th>
<th>Risk of Fatal Bleeding Event Cases per Patient-Year</th>
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<td>&gt;60</td>
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<td>Non-CNS</td>
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<td>110</td>
<td>62</td>
<td>36</td>
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<tr>
<td>Total</td>
<td>1817</td>
<td>571</td>
<td>240</td>
<td>183</td>
<td>49</td>
<td>31</td>
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</tbody>
</table>

* CNS indicates central nervous system; ellipses, not applicable.
† Patient-year at risk for major hemorrhage (platelet count <30 × 10^9/L); low estimate was based on median follow-up time; high estimate, on the maximum follow-up time.
‡ Risk was calculated as the ratio between the number of fatal bleeding events and the patient-year at risk.
§ This study reported the exact patient time at risk. Therefore, low and high estimates were not required.
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plain the discrepancy between the prevailing conception that ITP has a relatively benign course\(^3\) and the poor prognosis implied by our analysis.

**Implications of Uncertainties in Model Estimates**

Modeling the natural course of ITP required the use of several estimates. The stability of the models' results considering these uncertainties was verified by employing extensive sensitivity analysis, ie, examining the effect of varying these estimates along their plausible ranges.

**Estimating the Period at Risk for Hemorrhage.** Since the exact period of patient observation was not reported in most studies, we used an average between 2 extreme patient time estimates. When the model is set to the low estimates for bleeding risk, a loss of 11.15 QALY is predicted (36.21−25.06); setting high estimates yields a loss of 16.32 QALY (36.21−19.89) (Table 2). According to the base case analysis, a 30-year-old patient with ITP is predicted to lose 14.24 QALY (36.21−21.97).

**Age-Adjusted Bleeding Risk.** The quantitative estimation of the excessive risk for major bleeding among the elderly, relative to young patients, was based on the study by Cortelazzo et al.\(^4\) Another series that included a large elderly cohort\(^12\) supported this finding: a rate of 0.2 fatal bleeds per patient-year was found, compared with 0.016 to 0.042 per patient-year in the general pooled analysis (Table 1). When a constant bleeding rate was assumed (0.028 fatal bleeding events per patient-year), the model predicted a loss of 18.02 QALY. When less extreme differences in relative bleeding risks between age groups were used, the predicted prognosis was found to be worse than the basic model assumption, consisting of losses of 15.1 to 18.5 QALY. The reason is that by shifting the risk to a younger age, more events will happen earlier in life when they have a greater impact on remaining LE. Thus, assuming a relatively large effect of advanced age on the bleeding risks was a conservative assumption.

Finally, our age adjustment calculations were based on the relative risks in 3 age groups only, an insufficient number of points for reliable analytic curve fitting. We therefore approximated by using linear interpolations, though the true effect of age is probably not linear. Using an exponential curve instead of linear interpolation had only a small effect on the results (Table 2). Thus, varying the bleeding risks between the extreme conceiv...
able estimates based on our data pooling, as well as modifying our assumptions on age adjustment, does not change our main finding, ie, a substantially worsened prognosis due to ITP with low platelet counts.

**Extrapolations From the Literature.** Additional estimates of probabilities and utilities in the model were based on extrapolations from analogous scenarios in patients without ITP (eg, outcomes of hemorrhagic stroke in the general population). It should be emphasized that our findings concerning the grave prognosis of ITP in terms of compromised LE are completely independent of these extrapolations. The extrapolated estimates are used solely for allowing supplementary calculations of outcomes in terms of QALY. These estimates were obtained from the published medical literature. This extrapolation might have introduced some inaccuracy; however, there is no better evidence available. To examine the effect of potential inaccuracies in these parameters, we examined them over a wide range in sensitivity analyses. The effect of varying these parameters within a plausible range was minimal (Table 2).

**CLINICAL IMPLICATIONS OF FINDINGS**

The results of our analysis are quite surprising, considering the prevailing conception that ITP has a relatively benign course. While the LE of an “average” patient with ITP seems to be only mildly compromised, our model indicates that this might not apply for patients with persistently low platelet counts. Considering the consistency of the evidence and the stability of the models’ results despite uncertainties in the estimates used, we believe that these conclusions regarding the poor prognosis of ITP with persistently low platelet counts should not be ignored. Because there are multiple effective interventions available for the treatment of ITP, this new evidence of poor prognosis should strongly influence the aggressiveness of clinical management. This issue is of special importance in cases where the benefits of intervention are weighed against substantial adverse effects or risks, ie, high operative risk for splenectomy or corticosteroid dependency with associated adverse effects.

In this article, our main purpose was to estimate the quantity of LE loss due to ITP, and we did not particularly focus on modeling the effect of any specific therapy or sequence of therapies on ITP. Nevertheless, our model provides some insight about the potential effects of these treatments on LE and QALE in ITP. These effects can be achieved by modifying the probability for remission in the current model. We examined the effect on LE and QALE.

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**Table 2. ITP Markov Model Sensitivity Analyses**

<table>
<thead>
<tr>
<th>Aspect of Analysis</th>
<th>Model Estimate</th>
<th>Range Examined</th>
<th>Predicted QALE</th>
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<tbody>
<tr>
<td>Base case analysis</td>
<td></td>
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</tr>
<tr>
<td>30-year-old women with ITP</td>
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<tr>
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<tr>
<td>Variable</td>
<td></td>
<td></td>
<td>19.89-25.06</td>
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<tr>
<td>Bleeding risk†</td>
<td>Average rate</td>
<td>Low-high rates</td>
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<tr>
<td>Spontaneous remission</td>
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<td>0.0005-0.002</td>
<td>21.66-22.28</td>
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<tr>
<td>Disability rate among stroke survivors</td>
<td>30%</td>
<td>15%-50%</td>
<td>22.41-21.47</td>
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<tr>
<td>Mortality rate of hemorrhagic stroke</td>
<td>40%</td>
<td>20%-50%</td>
<td>20.84-22.25</td>
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<td>Proportion of CNS bleeding events among ITP fatal bleeding events</td>
<td>0.79</td>
<td>0.5-0.9</td>
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<tr>
<td>Disability coefficient due to disabling stroke‡</td>
<td>0.5</td>
<td>0.3-0.7</td>
<td>21.60-22.34</td>
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<tr>
<td>Disability coefficient due to presence of ITP‡</td>
<td>0.98</td>
<td>0.9-1</td>
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<td>Relative risks among age groups, &lt;40 y:40-60 y:60 y</td>
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<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td>Use of an exponential analytic curve¶</td>
<td>. . .</td>
<td>20.42</td>
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*ITP indicates idiopathic thrombocytopenic purpura; QALE, quality-adjusted life expectancy (see “Modeling the Natural Course of ITP” subsection in “Patients and Methods”); CNS, central nervous system; and ellipses, not applicable.
†The model uses an average set age-adjusted bleeding risk of low and high estimates from pooled analysis; see “Selection of Studies for Pooled Analysis” subsection in “Patients and Methods.”
‡See the “Health State Utilities” section in “Probabilities and Utilities” subsection in “Patients and Methods.”
§Analysis based on research by Cortelazzo et al. See Appendix.
¶Constant risk, no adjustment.
¶Annual bleeding rate = 0.0004 × exp(0.0762 × age).
QALE when this probability is set to 64%, which was estimated as a lifetime chance of recovery in ITP (spontaneous or in response to therapy) by George and Raskob.1 We assumed this remission occurs throughout the first 2 years of model simulation. Under these conditions, the model predicted that a 25-year-old female patient with ITP will lose only 5.4 QALY (40.3–34.9) and 7.4 years of life (54.5–46.9), compared with a predicted loss of 14.9 QALY and 20.5 years without intervening in the natural history of the disease. This is a slight overestimate of the treatment benefits, because the effect of the treatment complications on LE and QALE was not modeled. However, it seems that based on the bleeding risks derived in this study, the effect of treatment on patients with ITP has a major favorable impact on the course of the disease.

CONCLUSIONS

According to our model, patients with ITP and persistent low platelet counts have a poor prognosis. There is a discrepancy between these conclusions and the prevailing conception regarding the benign course of ITP. Thus, the model would suggest taking an active therapeutic approach in the management of ITP, perhaps more active than that currently practiced. Inherent limitations in the quality of existing evidence (retrospective series) prevent definitive management recommendations; however, we believe that multiple retrospective ITP series, which converge toward a consistent estimate of the treatment benefits, because the effect of the treatment complications on LE and QALE was not modeled. Therefore, it seems to base on the bleeding risks derived in this study, the effect of treatment on patients with ITP has a major favorable impact on the course of the disease.

APPENDIX

ESTIMATION OF AGE-ADJUSTED BLEEDING RISK

The age-adjusted risk for fatal bleeding among patients with a platelet count lower than 30 × 10⁹/L due to ITP was estimated according to the following considerations:

- Relative risks for major bleeding event in patients with chronic ITP, at age groups younger than 40, 40 to 60, and older than 60 years were based on the findings of Cortelazzo et al3:

  \[
  \text{BR}_{\text{agroup}} / \text{BR}_{<40} = 2.8
  \]

  and

  \[
  \text{BR}_{>60}/\text{BR}_{<40} = 28.9,
  \]

  where \( \text{BR}_{\text{agroup}} \) indicates the bleeding risk of patients with ITP within that age group.

- Duration of follow-up period was assumed to be independent of age.

- The likelihood of a patient with ITP to be thrombocytic at a given moment was assumed to be independent of this patient’s age. That is, a constant proportion of the patient observation time, \( r \), comprises the “at-risk patient time” (time when platelet count <30 × 10⁹/L) in the 3 age groups:

  \[
  \text{PY}_{\text{agroup}} = r \times \text{N}_{\text{agroup}}
  \]

  where \( \text{PY}_{\text{agroup}} \) indicates the patient time at risk of that age group; \( \text{N}_{\text{agroup}} \) the number of patients in the age-group; and \( r \), a constant. (The last 2 assumptions introduce some bias; however, they were unavoidable in performing age adjustment based on the available data. We accounted for this bias in the model by allowing wide ranges for sensitivity analyses.)

- Studies that reported the age distribution of the cohort were selected for this subanalysis. The total number of fatal bleeding events in these studies was determined. We assumed that the patient time contributed by each age group was proportionate to the relative size of each such group:

  \[
  \text{PY}_{\text{agroup}} / \text{PY}_{\text{Total}} = \frac{r \times \text{N}_{\text{agroup}}}{r \times \text{N}_{\text{Total}}}
  \]

  For 3 possible age groups (<40, 40-60, >60 years), \( \text{PY}_{\text{agroup}} \) indicates the patient time at risk contributed by each age group, the unknowns of our equations; \( \text{PY}_{\text{Total}} \) the total patient time (within the pooled studies), and \( \text{N} \), the number of patients.

- Finally, the bleeding risk within each age group was calculated as the ratio between fatal bleeding events and patient time of each group:

  \[
  \text{BR}_{\text{agroup}} / \text{BE}_{\text{agroup}} = \frac{\text{BE}_{\text{agroup}} / \text{PY}_{\text{agroup}}}{\text{BE}_{\text{Total}} / \text{PY}_{\text{Total}}}
  \]

  where \( \text{BE}_{\text{agroup}} \) indicates the bleeding risk adjusted for the age group; \( \text{BE}_{\text{Total}} \), the number of fatal bleeding events of this age group; and \( \text{PY}_{\text{agroup}} \), the patient time at risk contributed by the age group.

Solving the set of linear equations 1 through 6 yields the age-adjusted absolute risks \( \text{BR}_{\text{agroup}} \) for age groups younger than 40, 40 to 60, and older than 60 years.

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Reprints: Yael Cohen, MD, Gertner Institute for Epidemiology and Health Policy Research, The Chaim Sheba Medical Center, Tel Hashomer, Israel (e-mail: coheny@post.tau.ac.il).

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