Long-term Outcome of 231 Patients With Essential Thrombocythemia

Prognostic Factors for Thrombosis, Bleeding, Myelofibrosis, and Leukemia

Chor-Sang Chim, MD, FRCP, FACP; Yok-Lam Kwong, MD, FRCP, FRCPath; Albert Kwok-Wei Lie, FRCP, FRCPath; Siu-Kwan Ma, FRCP, FRCPath; Chi-Chung Chan, MRCP; Lap-Gate Wong, MRCP; Bonnie Chi San Kho, MRCP; Harold-Kwok Lee, MRCP; Joyceylyn Pui-Yin Sim, MRCP; Cheuk-Hung Chan, FRCP; Joyce Chee-Wun Chan, FRCP; Yiu-Ming Yeung, FRCP; Martin Law, PhD; Raymond Liang, MD, FRCP, FRACP

Background: Essential thrombocythemia (ET) is a clonal myeloproliferative disease associated with thrombohemorrhagic complications and myeloid transformation to diseases such as myelofibrosis and acute myeloid leukemia.

Methods: A multicenter study was conducted among 231 consecutive Chinese patients with ET. The literature about leukemogenic risk associated with the use of hydroxyurea therapy was reviewed.

Results: The median patient age was 65 years. Thrombosis rates at and after diagnosis of ET were comparable to those of white patients, but bleeding rates at and after diagnosis were much lower. The projected 10-year thrombosis-free, bleeding-free, and overall survival rates were 66%, 83%, and 80%, respectively. There were no deaths among patients 60 years or younger during a maximum follow-up of 15 years, and splenomegaly at diagnosis of ET appeared to protect against thrombosis. In multivariate analysis, advanced age predicted inferior 10-year thrombosis-free and overall survival, and male sex predicted inferior bleeding-free survival. Half the deaths were related to ET. The probability of myelofibrosis transformation was 9.7% at 10 years. Prior myelofibrosis (P = .008) and the use of melphalan treatment (P = .002) were risk factors for acute myeloid leukemia evolution.

Conclusions: Essential thrombocythemia is a benign disease of older persons. Chinese patients have a low risk of bleeding, and prior myelofibrosis is a major risk factor for evolution to acute myeloid leukemia. Leukemic transformation with hydroxyurea therapy alone is rare and warrants further prospective studies.

Arch Intern Med. 2005;165:2651-2658

Essential thrombocythemia (ET) is a clonal myeloproliferative disease involving a hemopoietic stem cell and manifesting predominantly as thrombocytosis. However, extreme skewing of X chromosome inactivation mimicking clonal hemopoiesis in healthy older women and polyclonal hematopoiesis in some patients with ET sometimes confound the diagnosis. Therefore, until a reliable clonal marker is available, ET remains a diagnosis by exclusion and has to be distinguished from reactive thrombocytosis and other chronic myeloproliferative diseases with prominent thrombocytosis and from myelodysplastic syndrome (MDS). In particular, ET should be distinguished from Philadelphia chromosome-positive chronic myeloid leukemia, which inevitably transforms into acute leukemia if not treated properly. Moreover, distinction from iron depletion in polycythemia vera (PV) is important, as iron deficiency may mask the polycythemia.

Essential thrombocythemia may transform into other Philadelphia chromosome-negative myeloproliferative diseases, including PV, myelofibrosis (MF), and acute myeloid leukemia (AML) or MDS. However, ET is generally considered a benign illness because it is associated with prolonged survival and a low risk of leukemic transformation. Thrombosis and, less frequently, bleeding are complications of the disease because of inherent platelet dysfunction. The long-term outcome of ET has been described largely among white patients but not among Chinese patients. Moreover, the leukemogenic potential of hydroxyurea, the main agent in the treatment of ET, has been controversial. In this study, we conducted a multicenter study to define the clinical characteristics, long-term outcome (survival and transformation to AML or MF), and risk factors for thrombosis among 231 patients.
Chinese patients with ET, most of whom were receiving hydroxyurea as the sole treatment.

**METHODS**

**PATIENTS AND DIAGNOSIS**

Two hundred thirty-one consecutive Chinese patients with ET were identified from the patient record systems in 5 regional hospitals in Hong Kong. Patient records were reviewed for demographic data, initial symptoms, treatment, and subsequent clinical course, including thrombosis, bleeding, and conversion to MF, PV, or AML. Diagnosis of ET was based on the revised Polycythemia Vera Study Group criteria, including persistent thrombocytosis with a platelet count higher than 600×10^3/µL and exclusion of reactive causes, MDS, Philadelphia chromosome–positive chronic myeloid leukemia, and other Philadelphia chromosome–negative myeloproliferative disorders (by hematocrit reading <40%, normal marrow iron store, and absent or minimal marrow fibrosis). In addition to evaluation of marrow iron, iron status was assessed by serum ferritin and serum iron levels and by total iron-binding capacity. The presence of the Philadelphia chromosome was detected by karyotyping, fluorescence in situ hybridization, or reverse transcription–polymerase chain reaction. A diagnosis of subsequent conversion to MF was based on the presence of marrow fibrosis and splenomegaly, a leukoerythroblastosis, and teardrop red cells, in addition to exclusion of secondary causes of MF. The diagnoses of AML and MDS were made according to the French-American-British classification. Recently, a prefibrotic phase of MF has been proposed that has a specific megakaryocyte morphologic structure, demonstrates a markedly increased propensity to MF, and is associated with inferior survival. For patients who developed MF, diagnostic bone marrow aspirates were reviewed to identify the characteristic morphologic features of abnormal megakaryopoiesis (grouping of cells containing compact bulbous nuclei, accompanied by bizarre features of differentiation). The initial treatment was according to the discretion of the attending physicians. In general, hydroxyurea would be started if patients were symptomatic or were initially seen with a platelet count higher than 1000×10^3/µL. The target platelet count was lower than 600×10^3/µL. Low-dose aspirin (100 mg/d) therapy would be started if there was a history of arterial events, including ischemic heart disease, thrombotic strokes, transient ischemic attacks, peripheral vascular disease, and erythromelalgia, or a history of venous thrombosis.

**DEFINITIONS AND STATISTICAL ANALYSIS**

Thrombotic events included arterial events (thrombotic strokes, transient ischemic attacks, and digital gangrene) and venous thrombosis (pulmonary embolism, deep venous thrombosis, reti-
nal venous thrombosis, and portal vein thrombosis). The mean hemoglobin levels and platelet and leukocyte counts at diagnosis were compared between patients initially seen with erythromelalgia and patients who were asymptomatic. Bleeding events included gastrointestinal tract bleeding, intracerebral hemorrhage, and soft tissue hematomas. The mean platelet count was compared between patients who had and those who did not have bleeding at diagnosis. All thrombotic and bleeding episodes at diagnosis and during follow-up were counted as events. Age, sex, prior MF, and platelet and leukocyte counts at diagnosis of ET were analyzed for their association with the development of AML and MF. Categorical variables (sex, smoking history, splenomegaly at diagnosis, and prior MF) between subgroups were compared using the χ² test or Fisher exact test, and the means of continuous variables (age and platelet and leukocyte counts at diagnosis) were compared using the t tests.

Thrombosis-free survival (TFS) and bleeding-free survival (BFS) were calculated from the date of diagnosis to the date of event. Overall survival (OS) was calculated from the date of diagnosis to the date of death or last follow-up. Survival curves were plotted by means of the Kaplan-Meier method and compared using the log-rank test. To study if thrombosis at diagnosis predicted subsequent thrombosis, TFS between patients initially seen with and those who did not have thrombosis was compared. Univariate analysis of age, sex, smoking history, splenomegaly at diagnosis, and high platelet count (>1200 × 10⁹/µL) and high leukocyte count (>11 000/µL) at diagnosis was performed to assess the effect of these variables on TFS, BFS, and OS. Multivariate analysis of prognostic factors (age, male sex, smoking, splenomegaly at diagnosis, and high platelet and leukocyte counts at diagnosis) for TFS, BFS, and OS was performed by means of the Cox proportional hazards model (using SPSS for Windows, version 12; SPSS Inc, Chicago, Ill). All P values were 2-sided, with P <.05 considered statistically significant.

RESULTS

PATIENTS AND TREATMENT

Demographic data are given in Table 1. One hundred thirty-four patients (58.0%) were older than 60 years. Two hundred nine patients (90.5%) started hydroxyurea at diagnosis of ET, although all patients were eventually exposed to hydroxyurea for variable periods. Hydroxyurea was the sole cytoreductive treatment in all patients except 9, who were treated with radioactive phosphate.
rus (3 patients), melphalan (4 patients for 6 months to 7 years), and anagrelide hydrochloride (2 patients) during their clinical course.

**THROMBOHEMORRHAGIC EVENTS AND RISK FACTORS**

Twenty-three patients (5.6%) initially had erythromelalgia at diagnosis (Table 2). There was no difference between the mean platelet count ($934 \times 10^3/\mu L$ vs $1001 \times 10^3/\mu L$, $P = .28$) and the mean leukocyte count ($11,100/\mu L$ vs $12,000/\mu L$, $P = .55$) at diagnosis for patients who had and those who did not have thrombosis at diagnosis. In particular, there was no significant difference in the mean platelet counts at diagnosis between patients with vs without erythromelalgia ($1034 \times 10^3/\mu L$ vs $988 \times 10^3/\mu L$, $P = .66$). The projected TFS was 66% at 10 years (Figure 1A). In univariate analysis, advanced age was associated with lower TFS ($P = .07$) (Figure 1B), and splenomegaly at diagnosis was negatively associated with thrombosis ($P = .02$) (Figure 1C) (Table 3). In multivariate analysis, only advanced age ($>60$ years) was associated with TFS (hazard ratio, 1.03; 95% confidence interval, 1.01-1.05; $P = .01$). The projected 5-year TFS did not differ for patients who had and those who did not have thrombosis at diagnosis (90% vs 76%, $P = .16$) (Figure 1D). The projected 10-year BFS was 83% (Figure 2A). In univariate analysis, factors associated with bleeding included male sex ($P < .01$) (Figure 2B), advanced age ($P = .07$) (Figure 2C), and high platelet count ($P = .07$) and high leukocyte count ($P = .07$) at diagnosis (Table 3). In multivariate analysis, only male sex was associated with inferior BFS (hazard ratio, 3.74; 95% confidence interval, 1.22-11.47; $P = .02$).

**MYELOID TRANSFORMATION AND RISK FACTORS**

**Myelofibrosis**

Seven patients developed MF after a median latency of 8 years (latency range, 4-12 years), 2 of whom developed AML (Table 4). Age, sex, and mean platelet count at diagnosis did not significantly affect the risk. The cumulative probability of MF transformation was 9.7% at 10 years.

**AML and MDS**

Five patients developed AML (4 patients) or erythroblastic refractory anemia (1 patient) after a median latency of 10 years (latency range, 2-14 years) (Table 5).
Three patients who developed AML received hydroxyurea only, and the other 2 received melphalan for variable periods in addition to hydroxyurea. Prior MF (P = .008) and melphalan exposure (P = .002) were risk factors for evolution to AML.

CAUSE OF DEATH, OVERALL SURVIVAL, AND RISK FACTORS

Twenty patients (age range, 62-90 years) died. Besides unknown causes in 2 patients, causes of death included AML or MDS (3 patients), MF (2 patients), bleeding (2 patients), thrombosis (2 patients), carcinoma (3 patients), and unrelated causes (4 patients from pneumonia and 2 patients from chronic obstructive airway disease). The projected 10-year OS was 80% (mean survival, 156 months) (Figure 3A). Univariate analysis showed that advanced age (P < .01) (Figure 3B) and smoking (P = .02) (Figure 3C) were risk factors predicting inferior OS. In multivariate analysis, advanced age was the sole risk factor predicting inferior OS (hazard ratio, 1.12; 95% confidence interval, 1.07-1.21; P < .001).

In contrast to other studies5-12 (Table 1) that reported a predominance of female patients, our study showed an equal sex prevalence among patients with ET. Moreover, a high percentage (54.1%) of our patients were asymptomatic at diagnosis, compared with 27% to 36% of patients in 3 other studies.6-11 Similar to other studies, our patients had an advanced median age, with 58.9% of our patients being older than 60 years. The mean platelet, leukocyte, and hemoglobin values at diagnosis of ET in our study were similar to those in other studies.5,7-9,11,12 Therefore, the clinical characteristics of Chinese patients with ET were similar to those of white patients with ET.5-12

Compared with other studies, our patients had a similar frequency of thrombosis at diagnosis but a lower rate of bleeding (Table 1). In an article evaluating 1850 patients enrolled in 21 retrospective studies, the frequency of thrombosis at diagnosis ranged from 9% to 84%, and the frequency of bleeding ranged from 4% to 63%.26 Similar to other studies, thrombosis was more common than bleeding among our patients (Table 2), and arterial thrombosis was more frequent than venous thrombosis.6,7,10-12 Moreover, advanced age,6,10,12 but not smoking,7,10,12 was a risk factor for thrombosis. Although prior thrombosis is an important risk factor for recurrent thrombosis,10,27 our patients who initially had thrombosis had marginally inferior TFS. In univariate analysis (P = .02) but not in multivariate analysis, splenomegaly at diagnosis seemed to protect our patients against thrombotic events. The spleen in untransformed ET sequesters platelets28 and may protect against excessive platelet count increases. In support of this, a randomized controlled study29 showed that patients with ET achieving lower platelet counts had a decreased incidence of thrombosis.

There were 22 episodes of bleeding in the present study, mostly from the gut (Table 2), with 2 fatalities. A high platelet count at diagnosis was predictive of bleeding at

<table>
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<tr>
<th>Table 4. Transformation to Myelofibrosis*</th>
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<tbody>
<tr>
<td>Patient No./Sex/Age, y</td>
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<tr>
<td>------------------------</td>
</tr>
<tr>
<td>1/M/52</td>
</tr>
<tr>
<td>2/F/65</td>
</tr>
<tr>
<td>3/F/72</td>
</tr>
<tr>
<td>4/M/44</td>
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<tr>
<td>5/F/51</td>
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<tr>
<td>6/F/47</td>
</tr>
<tr>
<td>7/M/62</td>
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*All patients received hydroxyurea only, except patient 2, who also received melphalan.

<table>
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<tr>
<th>Table 5. Transformation to Acute Myeloid Leukemia (AML) or Myelodysplastic Syndrome (MDS) Among Patients With vs Without Prior Myelofibrosis*</th>
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<tbody>
<tr>
<td>Patient No./Sex/Age, y</td>
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<tr>
<td>------------------------</td>
</tr>
<tr>
<td>1/M/52</td>
</tr>
<tr>
<td>2/F/65</td>
</tr>
<tr>
<td>3/F/42</td>
</tr>
<tr>
<td>4/F/78</td>
</tr>
<tr>
<td>5/M/84</td>
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*All patients received hydroxyurea.

Abbreviations: NA, not available; ND, not done.

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occurred. Seven patients developed MF after a median latency of 8 years, and 2 of them developed AML. Unlike PV, in which a phase of MF with myeloid metaplasia is well recognized, data on conversion of ET to MF are scant. In an extensive retrospective histopathologic study of chronic myeloproliferative disease, the risk of conversion to MF was 10% at 10 years. Another study showed the risk of MF to be 8.3% at 10 years, with a median latency of 8 years. Our results demonstrated a similar cumulative probability of MF conversion (9.3% at 10 years), with the same median latency of 8 years.

Five of 231 patients developed AML or MDS after a median latency of 120 months. Four patients received melphalan, 3 patients received radioactive phosphorus, and the remaining 224 patients received hydroxyurea only (at diagnosis or during follow-up). Therefore, the frequency of leukemic or MDS transformation among those receiving hydroxyurea as the sole treatment was 3 occurrences (1.3%) among 224 patients. In the literature, variable rates (1.3%-13.1%) of AML or MDS transformation have been reported. The rates were confounded by the inherent risk of leukemic transformation in ET and the variable use of alkylating agents, radioactive phosphorus, and hydroxyurea. Table 6 summarizes the transformation to leukemia or MDS among patients with ET receiving hydroxyurea as the sole treatment, with the frequency varying between 1.3% and 4.9%. 

Table 6: Rates of Leukemic Transformation

<table>
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<tr>
<th>Treatment</th>
<th>Rate of Transformation</th>
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<tbody>
<tr>
<td>Alkylating agents</td>
<td>1.3%</td>
</tr>
<tr>
<td>Radioactive Phosphorus</td>
<td>4.9%</td>
</tr>
<tr>
<td>Hydroxyurea</td>
<td>3.0%</td>
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</table>

Similar to these studies, our data showed a low frequency of AML or MDS transformation, with a prolonged latency in patients treated with hydroxyurea alone. In all of these studies, the use of alkylating agents or radioactive phosphorus was the only risk factor for AML or MDS transformation. Similarly, the present study showed a strong association between the use of melphalan and the development of AML (P = .002). However, AML has been reported in patients with sickle cell anemia treated solely with hydroxyurea. The leukemogenic potential of hydroxyurea is further implicated by the increased rate of “illegitimate” variable diversity joining in patients with sickle cell anemia who receive prolonged hydroxyurea treatment. Furthermore, previous investigations of PV showed that the risk of acute leukemia was not significantly increased until after 8 years of hydroxyurea exposure. This is particularly relevant because a substantial proportion of patients with ET (42.0% in our series) were 60 years or younger. Given that the median survival of the population in Hong Kong in 2003 was about 80 years (78.6 years for men and 84.3 years for women), hydroxyurea therapy may be required for more than a decade in younger patients who are diagnosed as having ET. Therefore, prospective studies are needed to address the leukemogenic potential of hydroxyurea therapy in ET, especially because anagrelide, a nonmutagenic platelet-lowering agent, is available as an alternative.

Two of our patients with AML or MDS transformation had prior conversion to MF. Previous findings have demonstrated higher rates (up to 20%) of leukemic transformation among patients with MF. Similarly, among patients with PV, patients who developed MF had a higher rate of leukemic transformation. This is further illustrated by a study in which almost half of the patients with acute leukemia evolving from PV had prior myeloid metaplasia.
eloid metaplasia. The frequency of AML or MDS transformation is much higher among patients who develop MF ($P = .008$). In contrast to the well-documented conversion of ET to MF or AML, sequential evolution of ET to AML after prior transformation to MF has only been reported in 6 cases.7,12,44-47 Although the platelet count at diagnosis was not associated with development of AML ($P = .39$), a high leukocyte count at diagnosis seemed to be associated with the subsequent development of AML or MDS ($P = .002$).

The mean survival in our series was 13 years, demonstrating the benign nature of ET. Moreover, despite a maximum follow-up of 15 years, there were no deaths among our patients 60 years or younger, suggesting that young patients with ET are likely to have a survival rate similar to that of age-matched control subjects. One study48 demonstrated that survival of patients with ET was comparable to that of age- and sex-matched healthy controls; however, another study showed that a high platelet count at diagnosis of ET negatively affected OS. Age, not platelet count, was the significant prognostic factor in our study. Moreover, death from thrombosis only occurred in 2 patients, which is much fewer than the rate of 29.8% reported previously.30

Because of the lack of an identified pathognomonic mutation, ET is largely diagnosed by exclusion. However, several independent researchers recently identified a somatic gain-of-function mutation in JAK2, a nonreceptor tyrosine kinase, in 65% to 97% of patients with PV and in 23% to 57% of patients with ET, resulting in a valine to phenylalanine substitution at position 617 (V617F).49-52 Because this mutation was found in patients but not in healthy controls, it serves as a specific marker of clonal myeloproliferative disease. Moreover, this mutation in a mouse model has been shown to result in constitutive activation of JAK2, leading to cytokine hypersensitivity and erythrocytosis,50 and is thus functionally important. The availability of this marker will facilitate future definitive diagnosis of ET.

In summary, ET among Chinese patients is a disease of older persons and has a benign clinical course. Advanced age is associated with inferior TFS, BFS, and OS. Conversion to PV and MF is uncommon. Leukemic transformation with hydroxyurea therapy alone is rare and has a long latency.

Accepted for Publication: June 27, 2005.
Correspondence: Chor-Sang Chim, MD, FRCP, FACP, Department of Medicine, Queen Mary Hospital, University of Hong Kong, 102 Pokfulam Rd, Hong Kong (jcschim@hkucc.hku.hk).

Financial Disclosure: None.

Acknowledgment: We thank Li-Chong Chan, PhD, FRCP, FRCPath; Clarence Lam, FRCP; Kit-Fai Wong, FRCP, FRCPath; Raymond Chu, FRCP, and S. C. Szeto, FRCP, FRCPath, for their help in ET diagnosis, and Stanley Yeung for his statistical advice.

Table 6. Comparison of Myeloid Transformation to Myelofibrosis (MF), Myelodysplastic Syndrome (MDS), Acute Myeloid Leukemia (AML), and Polycythemia Vera (PV) Among Studies

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</thead>
<tbody>
<tr>
<td>Transformation to AML/MDS</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>4/1</td>
<td>2/0</td>
<td>1/0</td>
<td>NA</td>
<td>12/0</td>
<td>6/11</td>
<td>1/0</td>
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<tr>
<td>Overall No. (%)</td>
<td>5 (2.1)</td>
<td>2 (2.1)</td>
<td>1 (1.3)</td>
<td>NA</td>
<td>12 (13.1)</td>
<td>17 (4.8)</td>
<td>1 (1.4)</td>
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<tr>
<td>Hydroxyurea only, No./total (%)</td>
<td>3/224 (1.3)</td>
<td>2/80 (2.5)</td>
<td>1/77 (1.3)</td>
<td>NA</td>
<td>1/22 (4.5)</td>
<td>7/201 (3.5)</td>
<td>1/32 (3.1)</td>
</tr>
<tr>
<td>Latency, median, y</td>
<td>10</td>
<td>9</td>
<td>6</td>
<td>NA</td>
<td>NA</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Hydroxyurea and AA: 2/4</td>
<td>AA: 0/19</td>
<td>Busulfan: 3/15</td>
<td>AA and phosphorus: 4/34</td>
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<td>Hydroxyurea, AA, and phosphorus: 5/7</td>
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<td>Hydroxyurea, AA, and phosphorus: 1/21</td>
<td>Busulfan: 2/41</td>
<td>AA and phosphorus: 0/12</td>
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<tr>
<td>Anagrelide hydrochloride: 0/2</td>
<td>None: 0/5</td>
<td>Hydroxyurea and other: 7/50</td>
<td>None: 1/7</td>
<td>Hydroxyurea and other: 7/50</td>
<td>Anagrelide: 0/29</td>
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<tr>
<td>Transformation to MF</td>
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<tr>
<td>No.</td>
<td>7</td>
<td>3</td>
<td>NA</td>
<td>13</td>
<td>6</td>
<td>NA</td>
<td>3</td>
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<td>Latency, median, y</td>
<td>8</td>
<td>5.8</td>
<td>NA</td>
<td>8</td>
<td>NA</td>
<td>NA</td>
<td>3</td>
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<tr>
<td>Transformation to PV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>0</td>
<td>0</td>
<td>NA</td>
<td>NA</td>
<td>3</td>
<td>NA</td>
<td>2</td>
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Abbreviations: AA, alkylating agents; NA, not available.

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