Glutathione S-transferases (GSTT1 and GSTM1) genes polymorphisms and the treatment response and prognosis in Chinese patients with de novo acute myeloid leukemia

Zhijian Xiao a,b,*, Lin Yang a, Zefeng Xu b, Yue Zhang a, Liang Liu a, Ling Nie a, Lin Li a, Jianxiang Wang a,c,**, Yushu Hao b

a State Key Laboratory of Experimental Hematology, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, 288 Nanjing Road, Tianjin 300020, China
b 6th Department of Clinical Hematology, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, 288 Nanjing Road, Tianjin 300020, China
c 2nd Department of Clinical Hematology, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, 288 Nanjing Road, Tianjin 300020, China

Received 16 September 2007; received in revised form 15 October 2007; accepted 15 October 2007
Available online 26 November 2007

Abstract

We investigated the prognostic significance of genetic polymorphism for glutathione S-transferase theta 1 (GSTT1) and glutathione S-transferase mu 1 (GSTM1) in 254 Chinese patients with de novo acute myeloid leukemia (AML) other than AML-M3. The early death rate after the initiation of chemotherapy was similar between the GSTT1+/GSTM1+ group and GSTT1−/GSTM1− group. The complete remission (CR) rate was higher in GSTM1+ group than in GSTM1− group (OR = 1.88; P = 0.03) after the first course of chemotherapy, and was higher in GSTT1+ group than in GSTT1− group (OR = 2.20; P = 0.02) after the second course of chemotherapy. Overall survival and disease-free survival of CR patients in GSTT1 and GSTM1 double present group was better than in GSTT1- and/or GSTM1-group (P = 0.03 and 0.02, respectively). Our preliminary results warrant testing of a larger number of patients.

Keywords: Acute myeloid Leukemia; Glutathione S-transferase; Polymorphism; Prognosis

The glutathione S-transferase theta 1 (GSTT1) and glutathione S-transferase mu 1 (GSTM1) genes are polymorphic in humans. A homozygous for non-functional allele causing a GST-null genotype will result in a loss of the enzyme activity. A number of prior studies [1–6] have reported on the relationship between GST genotype and treatment outcome in acute myeloid leukemia (AML). The null genotype of GSTT1 was associated with inferior overall survival (OS) in childhood AML [2]. In adult AML patients with GSTM1-null genotype had a trend toward a poorer survival than those with present alleles, but no such effects for GSTT1 and GSTP1 genotypes [5]. In a study of 106 adults with AML, GST-null genotypes were associated with poorer OS and early death rates after the initiation of chemotherapy were higher in the GSTT1-null group than the GSTT1 present group, with no effects for GSTM1 genotype [4]. Weiss et al. [1] reported that they found no statistically significant associations between GST genotypes and treatment outcomes in AML patient. In this study, we...

* Corresponding author at: 6th Department of Clinical Hematology, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, 288 Nanjing Road, Tianjin 300020, China. Fax: +86 22 27219070.
** Corresponding author at: 2nd Department of Clinical Hematology, Institute of Hematology and Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, 288 Nanjing Road, Tianjin 300020, China. Fax: +86 22 27306542.
E-mail addresses: zjxiao@hotmail.com (Z. Xiao), wangjx@hotmail.com (J. Wang).
analyzed the prognostic significance of gene polymorphism of GSTT1, GSTM1 in 254 Chinese patients with de novo acute myeloid leukemia (AML) other than AML-M3.

1. Design and methods

This study was approved by the Ethical Committee of Institute of Hematology, CAMS and PUMC according to the guidelines of the Declaration of Helsinki and was conducted between October 1997 and September 2005. A total of 254 cases were entered and all of them were untreated previously. There were 157 males and 97 females, with a median age of 32 (15–75) years. The diagnosis was according to WHO criteria [7]. Of the 254 cases, 81 were AML with t(8;21) AML/ETO, 54 AML with inv(16) or t(16;16) CBF-β/MYH11, 4 AML with 11q23 abnormalities (MLL), 1 minimally differentiated, 3 AML without maturation, 44 AML with maturation, 17 acute myelomonocytic leukemia, 42 acute monocytic leukemia, and 8 acute erythroid leukemia. Patients with acute promyelocytic leukemia and those with AML secondary to prior chemotherapy, or to an antecedent hematologic malignancy were excluded.

All the patients were treated with HAD regimen as induction therapy, which consisted of homoharringtonine (HHT) 2.5 mg/m² intravenously on days 1–7, cytosine arabinoside (Ara-C) 150 mg/m²/d continuous infusion on days 1–7, and daunorubicin (DNR) 45 mg/m² intravenously on days 1–3. The second course of HAD induction therapy was applied to patients who were not in complete remission (CR) after the initial course of induction therapy. Postremission therapy consisted of HA regimen (HHT and Ara-c) (course 1 and 4), DA regimen (DNR and Ara-c) (courses 2 and 5), and MA regimen (MTZ and Ara-c) or HAM (Ara-c 1 g/m², q12h, intravenously on days 1–4, combined with MTZ 8 mg/m², intravenously on days 5–7 (courses 3 and 6).

DNA was extracted from peripheral blood or bone marrow cells by a standard phenol/chloroform method. DNA was dissolved in 10 mmol/L Tris–HCl-I mmol/L EDTA (pH 8.0), stored at 4°C, and quantitated with spectrophotometry at 260 nm. The multiplex PCR method report by Chen et al. [8] was used to simultaneously amplify and analyze GSTM1, GSTT1, and β-globin from patients. The PCR products were electrophoresed on 2% (w/v) agarose gel. The size of each product was 269bp, 480bp, and 268bp for GSTM1, GSTT1 and β-globin, respectively. The absence of amplifiable GSTM1 or GSTT1 despite the presence of β-globin PCR product indicates the respective null genotype for each.

Survival probabilities were estimated by the Kaplan–Meier method, and differences in the distributions between the genotypes were evaluated using the log–rank test. OS was calculated from the first day of therapy to death. Disease-free survival (DFS) for patients who had achieved CR was measured from the date of CR to relapse or death. Relapse-free survival (RFS) was defined as the time from the date of CR to
relapse or death from progressive disease, censoring deaths from other causes.

2. Results and discussion

Of the 254 patients, 21 died before marrow recovery or adequate assessment of response. One hundred and sixty-five (68.5%) achieved CR after the first course of chemotherapy and 194 (80.5%) achieved a CR after the second course of chemotherapy. Median follow-up was 36 months (11–111 months). Until now, 104 patients were still alive, the other 138 patients died. Twelve patients lost to follow-up are censored at the date they were last known to be alive. The median OS and median RFS were 22 and 19 months, respectively. At 3 year and 5 year, the expected OS rates were 38.9 ± 3.5% and 25.2 ± 6.5%, and the expected RFS rates were 32.8 ± 3.9% and 22.4 ± 5.2%, respectively.

Patients with the GSTM1-present genotype had a higher CR rate compared with those with GSTM1-null genotype after the first course of induction chemotherapy ($P = 0.03$), and so did for the GSTT1-present genotype than the GSTT1-null genotype after the second course of induction chemotherapy ($P = 0.02$). The GSTM1 and GSTT1 double present genotype patients also had a higher CR rate than those with GSTM1-null and/or GSTT1-null genotype after the first course of induction chemotherapy ($P = 0.02$) (Table 1).

In the present study, there was no statistically significant association between GST genotypes and treatment outcomes in AML patients (Fig. 1A and B), which is in agreement with another study [1], but differ from other studies [3–5]. Autrup et al. [5] reported that patients with GSTM1-null genotypes had a trend toward a poorer survival than those with present alleles, with no effects of GSTT1 and GSTP1 genotypes. In a study of 106 adults with AML, GST-null genotypes were associated with shorter OS ($HR = 2.4$, 95% CI = 1.2–4.9) [3].
Another study [4] found that GSTT1-null genotypes were associated with poorer OS.

As to whether there is relation between GSTT1 and GSTM1 combined genotypes and prognosis, the results of our data analysis were as follows. The median OS of patients with GSTM1 and GSTT1 double present genotype was not reached until now and the median FRS of these patients was 43 months. The expected OS rate of patients with the GSTM1 and GSTT1 double present genotype was higher than those with GSTM1-null and/or GSTT1-null genotype at 3 year (50.1 ± 9.6% vs. 36.8 ± 3.8%) and at 5 years (50.1 ± 9.6% vs. 27.2 ± 4.6%) (log–rank P = 0.03) (Fig. 1C), and so did for the expected FRS rate in patients with the GSTM1 and GSTT1 double present genotype than in those with GSTM1-null and/or GSTT1-null genotype at 3 year (50.3 ± 10.0% vs. 29.2 ± 4.2%) and at 5 year (43.1 ± 9.6% vs. 15.7 ± 6.3%) (log–rank P = 0.02) (Fig. 1D).

In summary, in this study, we showed AML patients with deletions of GSTM1 or GSTT1 or both had a lower probability to achieve CR on induction therapy as compared to patients with intact GST genes and a shorter survival. As the sample size is small, these results may be attributable to chance and then should be confirmed in studies of larger collection of these patients.

Acknowledgements

Supported in part by Program for New Century Excellent Talents in University (NCET-05-0173), HIGH TECH RESEARCH AND DEVELOPMENT (863) PROGRAMME (2006AA02A405) and National Natural Science Funds (No. 30670899).

References