Effect of high-dose methotrexate chemotherapy on intestinal flora and mucosal barrier in children with acute lymphoblastic leukemia

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Abstract

Background: High-dose methotrexate (HDMTX) chemotherapy is generally accepted as an effective method for the treatment and prevention of extramedullary leukemia in children. However, it is unknown whether there are the damaged effect of HDMTX chemotherapy on intestinal mucosal barrier, which may in turn influence the progress or prognosis of leukemia. The levels of diamine oxidase (DAO) and endotoxin were measured to be able to evaluate the damaged intestinal mucosal barrier. The aim of this study was to study the effects of high-dose methotrexate (HDMTX) treatment on intestinal mucosal barrier in children with acute lymphocytic leukemia (ALL).

Objective: High-dose methotrexate (HDMTX) chemotherapy is generally accepted as an effective method for the treatment and prevention of extramedullary leukemia in children. However, it is unknown whether HDMTX chemotherapy kills intestinal bacteria and affects intestinal mucosal barrier on a large scale, thus causing dysbacteriosis and mucosal dysfunction, which may in turn influence the progress or prognosis of leukemia. The aim of this study was to examine changes in intestinal flora and intestinal mucosal barrier in children with acute lymphoblastic leukemia (ALL) treated with HDMTX chemotherapy.

Methods: Bacterial DNA in stool from 36 healthy children and 36 ALL children were extracted and tested at A260 with a spectrophotometer before and after HDMTX chemotherapy. The primers of Bifidobacteria, Lactobacillus and Escherichia coli were designed according to the 16SrRNA/DNA bacterial sequences. Bacteria were qualitatively and quantitatively confirmed by routine polymerase chain reaction (PCR) and fluorescent quantitative PCR, respectively. The blood samples were collected from 30 normal children and from 30 children with ALL after 1h, 24h, 44h and 68h of intravenous drip HDMTX. The levels of diamine oxidase (DAO) and endotoxin were measured by the spectrophotometer in the isolated plasma.

Results: Our data showed that the total amount of bacterial DNA in the stools of children with ALL was decreased by 29.6% compared with healthy children. The total amount of flora in the stools of children with ALL on the third and seventh days after chemotherapy were 1496.5±577.1 and 1966.6±598.3 ng/mL, respectively, which was notably less than before chemotherapy (2436.3±768.6 ng/mL) and healthy children (3479.3±870.5 ng/mL). The amount of Bifidobacteria, Lactobacillus and E. coli in the intestinal tract in the ALL group after chemotherapy had an apparent change, which decreased most clearly on the third day, and partially recovered on the seventh day after chemotherapy. The measured levels of plasma endotoxin and DAO in ALL group were significantly higher than in normal control group, the difference was statistically significant (P < 0.01). The level of plasma endotoxin and DAO after 24h and 44h were both higher than 1h and 68h IV drip HDMTX, and reach the peak after 24h, the difference was statistically significant (P < 0.01).

Conclusions: The amount of bacterial DNA, Bifidobacteria, Lactobacillus and E. coli in the stools was in decrease significantly compared with the control group. The levels of plasma endotoxin and DAO in ALL group were apparent higher than in normal control group. Leukemia itself and HDMTX chemotherapy can all cause intestinal dysbacteriosis and intestinal mucosal barrier dysfunction in children with ALL.