Observational studies on prophylaxis of hepatitis B virus reactivation with long or short course oral Agents among patients with acute myeloid leukemia

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Abstract: Background and purpose: hepatitis B virus (HBV) reactivation is one of serious complications among patients with acute myeloid LeukeMia (AML) following cytotoxic induction and consolidation chemotherapy. Nucleoside analogs including lamivudine and entecavir have been widely used as prophylactic or preemptive treatment for HBV reactivation. This study is to investigate clinical efficacy and safety of a long or short course oral ANTI-HBV for agents HBV reactivation in AML patients with HBV infection during chemotherapy. Methods: the medical records AML patients with HBV infection receiving a T least 4 courses of chemotherapy were

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There retrospectively identified and systematically analyzed. These patients were further divided into four groups according to their hepatitis B surface antigen (HBsAg) status prior to initiation of chemotherapy and duration of prophylactic therapy. Reactivation of HBV and toxicity profiles of oral antiviral agents were systematically analyzed and compared among different groups. Results: HBV reactivation and documented hbv-related hepatitis were significantly lower in AML patients under long course antiviral prophylaxis (i.e. continuing oral antiviral therapy for at least 6 months after cessation of chemotherapy, LCP group) than in the patients with short course antiviral (i.e. continuing oral antiviral therapy for one month after cessation of chemotherapy, SCP Group), which was 5.56% (1/18) and 0% (0/18) compared with 45.45% (5/11) and 36.36% (4/11) (p=0.018 and p=0.014). There was little difference in the incidence of antiviral resistance between LCP and SCP groups [11.11% (2/18) vs 9.09% (1/11), p=0.05]. Furthermore, the rates of HBV reactivation and hbv-related hepatitis were significantly lower in AML patients with Positive HBsAg (HBsAg >0.05 IU/ml) under long course antiviral prophylaxis than in HBsAg positive patients who received short course antiviral agents [8.33% (1/12) and 0% (0/12) vs 66.67% (4/6) and 66.67% (4/6), p=0.022 and p=0.005]. Meanwhile, there was little difference in the rates of antiviral resistance-LCP and SCP between groups HBsAg among patients [8.33% (1/12) vs 16.67% (1/6), p=0.05]. In addition, the rates of HBV reactivation and hbv-related hepatitis as so as antiviral resistance were shown to have little difference in AML patients with negative HBsAg (hbsag<0.05 IU/ml) between LCP and SCP groups. Concerning antiviral agent toxicity, no grade 3-4 toxicity occurred in patients from LCP or SCP group. Conclusion: Long course prophylaxis with oral antiviral agent appears to be an effective and tolerated preventative approach for reducing risks of HBV reactivation and associated events in AML patients with positive HBsAg during chemotherapy, which serves as a platform for the design of prospective clinical.

Keywords: Acute myeloid leukemia; Hepatitis B virus reactivation; Prophylactic antiviral therapy

Acute myeloid leukemia (Acute myeloid leukemia, AML) is a class of heterogeneous hematopoietic stem progenitor cells, malignant cloning Sexual disease, to anthracene ring drugs (like erythromycin and methoxy) erythromycin etc) Combined with cytosine-induced chemotherapy and the consolidated chemotherapy of high-dose chemotherapeutic
drugs after remission is AML. The primary treatment for is AML merge HBV-infected patients after chemotherapy hepatitis B virus (hepatitis B virus, HBV) re-activating can cause different degrees of liver dysfunction affect chemotherapy process, even causes fulminant hepatitis and endangers life. So, actively explore prevention AML merge HBV-sense Infected patients HBV virus reactivation. Effective policy is necessary for Sex and clinical significance. Recent research Discovery nucleoside anti HBV drug (including lamivudine and Grace Entecavir) prophylactic treatment can significantly reduce HBV re-activating risk. But these studies mainly focused on lymphoma patients receiving immunotherapy (1-3), in AML merge HBV-infected patients with prophylactic nucleoside class anti HBV Drug. Report still less, also about anti-HBV systemic study of drug use and timing is still missing. Viewon this, The study passes retrospective analysis example AML merge HBV infect and accept at least 4 Pro for patients undergoing chemotherapy bed data, explore nucleoside resistance HBV drug prevention virus again.

Live clinical efficacy and safety and the ideal course of treatment.

1. Data and methods

1.1 patients select

This study is for people Year 1 Month one 2016 Yearmonth period ninth People's Hospital affiliated to Shanghai Jiaotong University Medical School. The blood inside Example AML merge HBV infected and accepted at least 4 patients with chemotherapy, among men: Cases, women @ Example, age-year old, median age-year old. Specific person standard as follows: ① conforms to who (World Health Organization, who) myeloid tumor typing 2008 version AML Diagnostic Criteria; ② before chemotherapy HBV-related antigen, includes HBV surface antigen (hepatitis B surface antigen, HBsAg), eantigens and antibodies (hepatitis B antigen then hepatitis B antitbody, HBeAg and HBeab) and core antibody (hepatitis B core antitbody, Hbcab) serological detection results at least 1 Positive; ③ Imaging for cirrhosis-free and leukemia liver invasion ④ HBVDNA (hepatitis B virus deoxyribonucleic acid) Quantitative polymerase chain reaction (quantitative polymerase chain reaction, PCR) Check. The number of copies is less than or equal to 2x 10^6/mL; ⑤ liver function Quaranine Alanineaminotransferase (alanineaminotransferase, ALT), aspartic acid aminotransferase (aspartateaminotransferase, AST) and Total bilirubin no more than positive constant 1.5 Times; ⑥ excludes other neoplastic diseases, Immune Disorders, sick, Diabetes and obesity. i All patients accepted at least 4A course of induction and consolidation of chemotherapy, where induction chemotherapy is going toa Dextran combined with cytidine (idarubicin + cytarabine, IDA + Ara-C") IAScheme, that is, norepinephrine8–mg/(2. (/L), 1–3 Day, glycoprotein/mg/2. (/L), 1–7 Day, Dis1 Cycle; consolidates chemotherapy for large doses of sugar2–3/m², every H1 Times, 1, 3, 5 Day, Dis1 Cycle.

1.2 Research Methods

1.2.1 treatments and Groups

Induces chemotherapy at the startof, Synchronous Oral entecavir mg/d, at the same time giving patients support treatment based on patient taking anti-HBV drug duration is divided into two groups: ① Long course prevent (Long Course prophylaxis, LCP) Group oral anti HBV drugs continue until end of chemotherapy 6 months above; ② Short Session Prevention (short Course prophylaxis, SCP) Group, Port anti HBV drugs continue until chemotherapy ends 1 month less than at the same time. According to the patient HBsAg serological Detection results are divided into two Group: ① HBsAg Positive Group, refers to the patient's serum HBsAg Largo to equal to 0.05IU/ML; ② HBsAg Negative Group, is the patient Person Serum HBsAg less than 0.05IU/ML.

1.2.2 observe metrics and evaluation criteria

Collect people group patients before and after each chemotherapy cycle and chemotherapy History of follow-up visits, General physical Check, all blood cell count, coagulation indicator, Serum liver and kidney function index, serum HBV-related antigens and HBV-DNA Set amount (with fluorescence quantification PCR Method, detect lower-bound copies of 5.0x2a/mL) Clinical Data, system analysis and evaluation.
suffering person HBV reactivation rate, HBV associated hepatitis Burst rate, HBV treatment rate of primary drug resistance and the frequency of liver failure. Evaluation criteria such as:

1. HBV re-activate: Serum HBVDNA level baseline elevation > times or above, or lack of HBVDNA baseline. The absolute number of copies exceeded 2.0×10^6/mL, or person serum HBVDNA from negative to positive; 2. HBV related hepatitis. Outbreak: when ALT horizontal rise greater than 5 double positive constant. Upper limit; (3) HBV primary drug resistance: nucleoside (acid) simila-to Object Therapy Week, HBVDNA load descending less than L1 Log Ten IU/mL; (4) Liver failure: has ascites or other Portal Hypertension, hepatic encephalopathy (Type), serum total bilirubin greater than 51.3 wattol/L and albumin less than G/L; 4) prothrombin activity is less than or equal to 40%.

1.2.3 adverse reaction observation

observe and record adverse reactions: includes type, frequency and severity. Adverse Reactions Reference US National Cancer Research adverse reaction rating standard (National Cancer Institute Common Terminology Criteria for Adverse Events, NCI-CTCae) 4.03 version, and evaluates its relevance to the drug, where the drug in most common drug badeventfor creatine kinase (Creatine kinase, CK) elevation. Root under CK Horizontal 4 level: 1 level: (3~<5) xisina normal value; limited; 2 level: (5~<7) x Maximum normal value; 3 level: (7~<10) x Maximum normal value; 4 level greater than or equal to Max. Maximum normal value. 1.3 statistical processing.

All data takes the SPSS 13.0 Software Analysis, Count Capital material with ratio and composition ratio for, with/Validation comparison between groups, p < 0.05 is statistically significant for the difference.

2. knot Fruit

2.1 General clinical data for patients with long and short course of treatment group

LCP and SCP group patients are and one example, two groups of middle age, gender composition, AML T typing, Prognosis is divided into layer and induction and consolidation of chemotherapy sessions, Analysis Comparison, no significant difference (P > 0.05, Table 1).

2.2 patients with long-duration treatment group HBV re-activate and its related event incidence

LCP The Group has only 1 patient at the end of chemotherapy 3 Month appear HBV re-activate, reactivation rate 55.6% (1/18), and did not occur HBV associated hepatitis, SCP The Group has 5 example patient occurs HBV-Activate, where 3 The example occurs at the end of the chemotherapy 3~5 Month, 1 The example appears in the chemotherapy section 4 Session, another 1 Example Initial HBV-DNA negative patients in chemotherapy 4A session virus re-Activate, HBVT he total reactivation rate is 45.45% (5/11), this outside HBV associated hepatitis incidence is 36.36% (4/11). LCP

Group Patients HBV reactivation rate and the associated hepatitis burst rate are all significantly lower than SCP group patients (corpus = 0.018 and Corpus = 0.014), same as when LCP and SCP group patients ' HBV primary drug resistance rate 11.11% (2/18) and 9.09% (1/11). There is no statistically significant difference (corpus > 0.05).

Further subgroup analysis displays, LCP in the group HBsAg (+) Patients HBV the reactivation rate and the associated hepatitis burst rate are 8.33% (1/12) and 0% (0/12), and SCP in the group Example HBsAg (+) The patient occurs during chemotherapy HBV reactivation and concomitant hepatitis, other 3 case at the end of chemotherapy appears in the month HBV re-excitation Live with hepatitis, HBV reactivation rate and associated hepatitis burst rates are 66.67% (4/6), significantly higher than LCP Group HBsAg (+) patient (Corpus = 0.022 and the user = 0.005); at the same time, LCP and SCP Group HBsAg (+) Patients HBV The primary drug resistance rate is 8.33% (1/12) and 16.67% (1/6). There is no statistically significant difference (corpus > 0.05). another, LCP Group has 1 Example HBsAg (-) Patient send live HBV primary drug resistance, and SCP The Group has 1 Example HBsAg (-) Patient on chemotherapy page 4 session appears HBV and then activate, the but not concurrent liver inflammation, continue taking medication HBV-DNA drops again to the measured value with the under LCP and SCP Group HBsAg (-) Patients HBV reactivation Rate, hepatitis

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Incidence and primary resistance rate in theLCPGroup0% (0/6), 0%> (0/6) and 16.67%> 1/6); on SCPGroup to 20%> (1/5), 0% (0/5) and 0% (0/5), There is no statistically significant difference (P>0.05). The specific numeric and statistical analysis of the above subgroup analysis for is shown in the table 2.

2.3 adverse drug reactions in patients with long and short course of treatment group

LCP and SCP Group Patients 1~2 level CKelevated occurrence rate, respectively for 22.22%> (4/18) and 27.27%> (3/11), Difference No statistic meaning (P>0.05). Two groups of patients did not appear 3~4 level CKelevation to cause undesirable events to stop drugs. In addition, Two group of patients follow up The does not occur during the medication the Grace Entecavir related to 3 level above hematologyor non-hematological toxicity. No liver failure throughout the follow-up experience ((table 3). Two groups of patients with adverse reactions during chemotherapy the result of the reaction of the treatment drug factor. Interference no statistical comparison.

3. To askon

is currently, Blood tumor merge HBVinfectected patients with chemotherapyperson and period HBV re-activating issues getting heaviview [4], especially in China HBV people with high infection rates. The area is more closely watched. Clinical studies show, before and after chemotherapy and general monitoring of follow-up period HBV Serum related antigen and (or) HBVDNA level, and give prevention and preemptive treatment can significantly Lower patient HBV Reactivate Risk, To enable the patient to receive a clinical benefit [5]. Recent, Taiwan A large retrospective study shows, AML merge HBV virus reactivation after chemotherapy for infected patients not low, recommend giving patients nucleoside resistance HBV preventative Governance Therapy (4) Other research also finds, AML Patients HBV and then activate the less than A lymphoma patient receiving immune chemotherapy, same need to prevent antiviral treatment [7]. However, anti HBV Preventive treatment healing time, Selection Of course and antiviral drugs still not Clear and pending further study.

This study found that, Long Course drug prevention group AML Patients, HBV reactivation rate and associated hepatitis burst rates are significantly lower than short course prevention group patients, prompt AML Merge HBV infection patients with prophylactic antiviral therapy at least until the end of chemotherapy. 6 Month above, Although sample size is small, But this is reported at home and abroad Similar to the conclusions of clinical guidelines [8-10]. However, you must refer to out of still has I during Long course anti HBV medication cases appear virus reactivation, and the original drug resistance to the grace Entecavir, So, on anti HBV There is still a need to monitor the liver closely during the treatment features and plasma virus load. Once a virus recovery is found, consider HBV Show drug-resistant problems, detect virus mutations in a timely manner and adjust anti HBV medication also, This study also found, short session Preventive Medication Group, HBsAg (+) patient's HBV reactivate rate and associated hepatitis burst rates are significantly higher than long course of prevention Group HBsAg (+) Patients, prompts HBsAg (+) high-risk groupsto be treated with foot treatment HBV Preventative treatment session Insufficient can cause HBV reactivates and sudden hepatitis, This further certificate AML Merge HBsAg (+) patient prophylactic antiviral treatment necessity and HBsAg (-) The patient is treated with a duration of treatment HBV After preventive treatment HBV and then activate the hepatitis Outbreaks and primary drug resistance incidence no significant difference, description for HBsAg (-) patients are No need for a foot course antiviral therapy pending further study, other outside, has example HBsAg (-) patient with chemotherapy 4A session appears HBV re-activate, Prompt for induction or consolidation after chemotherapy AML patient's body HBV protective antibodies drop and cause virus to be stimulated again alive. so, HBsAg (-) patients are still required to monitor during chemotherapy measuring plasma virus load [11-12]. This study adverse drug reaction examination test results show, There is no in the medication group 3 level CKelevated level or toxic reaction, prompt for a card Wei as prophylactic anti-HBV drugs with good security and tolerated of course, This study is based on retrospective study of Nature and sample size still has limitations, There's room for further improvement.

Summary, AML Merge HBVinfectected patients save after chemotherapy on virus reactivation risk. Long course of oral
administration Entecavir isloweringAMLmergeHBsAgpositive infection patients after chemotherapy virusre-activation and virus-related event incidence valid and safesexual Good prevention regimen,Worth further forward-looking Research.

References


