Adverse Reactions of Pegaspargase for Acute Lymphocytic Leukemia

WANG Yue, LI Xue-rong△, ZHONG Ren, YANG Jin, SUN Li-rong

(Qingdao university medical college associated hospital pediatric haema-tology, 276003, Qingdao, China)

ABSTRACT Objective: To investigate the adverse reactions of the two common dosage forms of L-asparagine enzyme in the combination chemotherapy of acute lymphocytic leukemia. Methods: During January 2009 to December 2010, the children with acute lymphocytic leukemia received the chemotherapy concluding Vincristine, Pirarubicin, Asparaginase and Prednisone. The patients using pegaspargase which was the pegylation of L-asparaginase in VDPAP project were chosen as A group (40 cases), while the patients who using L- asparaginase in the past were chosen as B group(60 cases) . The adverse reactions were detected. During the anterior-posterior combination chemotheray, the hemogram, blood clotting function and the allergy were detected in the twenty-eighth day. Results: The allergy occurred in 2 patients in group A (5%) and 13 cases of allergy in group B (21.67%), P=0.045,which was statistically significant. The rest adverse reactions, including Leukopenia, neutropenia, thrombocytopenia, hypohemoglobinemia, hypoinosis, the extension of partial thromboplastin time, the reduction of antithrombin **III**, and the rise of alanine aminotransferase, hypoproteinemia, had no significant differences. The average hospital stay of the patients in the Group A is 11.14 days while in the Group B is 18.47 days. Conclusion: There is not much difference in adverse reactions of the two formulations of L-asparaginase ,but pegaspargase has the following advantages: less frequency of use, easy to use, low allergy, reducing the hospital stay.

Key words: Pegaspargase; Aute lymphocytic leukemia; E-coli form; L- asparaginase; Adverse reactions

Chinese Library Classification: R725.5, R733.71 Document code: A

Article ID:1673-6273(2011)14-2691-05

Introduction

L-ASP is one of the basic drugs in the combination chemotherapy of acute lymphocytic leukemia, which influence the long-term prognosis of the children directly, however, the chemotherapy were often interrupted duing to its clinical adverse reactions. So far, there are two common dosages form of L-asparagine: E. coli dosages form, Evolution of polyethylene glycol-based (Pegaspargase). Because E. coli-type is from Variant protein, it leads to a higher incidence of allergy. PEG-Asp has a low incidence of allergic reaction. However, its applications in pediatric patients at home are rarely reported. PEG-Asp were applied instead of E. coli -type in the ALL children's VDLD chemotherapy for the intensive therapy, the adverse reactions were observed.

1 Materials and method

1.1 General information and group

From 2009.3 to 2010.12 we admitted the ALL children who have been released. All of them are except for the dysfunction of heart, liver, kidney, and pancreas. Apply of PEG-Asp-type instead of E. coli L-ASP in VDLD chemotherapy of 40 patients for the Intensive therapy (VDLD group，Group A) compared with 60 patients with previous dosage form of E. coli, make a retrospective clinical controlled study. In Group A, the male: female was 1:1, ages from 2 to 13 years old, with a median age of 6.3 years old, SR-ALL 16 cases, MR&HR-ALL 24 cases; While in group B, male: female was 1:1.14, aged from 2.5 to 11.5 years old, with a median age of 6.7 years, SR-ALL 21 cases, MR&HR-ALL 39 cases.

1.2 Diagnosis and treatment standards of Leukemia

Adopt the diagnosis and treatment recommendations in children with acute lymphoblastic leukemia (The third draft revision) (2006)[1]and Grading of chemotherapy side effects adopt the side effects and countermeasures in cancer chemotherapy, divided into 0 ~ 4[2].

1.2.1 Treatment Program

All patients received Vincristine at a dose of 1.5mg/m^2 (max≤ 2mg) intravenously, at intervals of a week, four times totally. They also received Pirarubicin 30mg/m^2/time intravenously once a week, twice in all and took Prednisone 40 mg/m^2/d orally for three weeks then stopped gradually. The patients in Group B received E.coli type L-asparagine enzyme at a dose of 5000---10000μ/m^2 intramuscularly every other day for eight times, while the patients in Group A received Pegaspargase at a dose of 2500IU/m^2 intramuscularly once every 14 days for twice. Skin test must be taken before the patients receive L-ASP chemotherapy,the two dosage of forms can be used directly if the skin test was negative. For the patients received PEG-Asp who showed positive,we gave dexamethasone at a dose of 0.2mg/kg for 3 days before

Author: Wang Yue, femal, master, Mainly engaged in pediatric haema-tology research, Tel:13296391778,
E-mail gumenghuangshu@163.com
△Correspoonding author: LI Xue-rong, Tel:053282911313
(Received:2011-01-27 Accepted:2011-02-23)

chemotherapy;for those received E. coli-type who showed positive,we gave desensitization [3] therapy before chemotherapy. hepatoprotective drugs, H2 receptor blockers, central antiemetic drugs and calcium were added. All the patients shoud have the low-fat diet for 3 days before chemotherapy and a week after chemotherapy, then gradually return to normal diet. Give component blood transfusion to the children when they had coagulation defects, anemia and thrombocytopenia, use G-CSF 5μg/kg/d,iH,for the children in bone marrow restrained phase and with ANC<1.0× 10^9/L until the ANC is more than1.0× 10^9/L, give anti-infection and other support treatment when the hypoproteinemia and infection exist.

1.3 indexes

The blood routine test, amylopsin in serum and urine, blood coagulation function and blood glucose were detected every 3 days, liver function was detected every 7 days during chemotherapy until the 28th day. Bone marrow examination was done PEG before and after chemotherapy; The hypersensitivity reactions and other adverse reactions were observed; make a statistic of the hospital stay.

1.4 Statistical analysis

By SPSS17.0 statistical software, classification count data such as blood routine test and hemagglutination routine test was done by rank sum test, the rest use chi-square test, P<0.05 was statistically significant.

2 Results

2.1 Allergic reactions

Before L-asp chemotherapy, skin test should be taken. Group A: positive skin test, 2cases(5%) (in the first dose 0 case appear allergic;in the second dose 2 cases appear allergic) ;Group B:13 cases(21.67%),P=0.045 was statistically significant. During medication process, 1 patient of allergy in Group A showed a transient scattered rash; In Group B 2 patients of allergy manifested as lips and throat swelling, 1 patient with scattered rash and itching for 5 days, 1 patient with persistent diarrhea accompanied by rash for a week. The remaining patients of allergy only showed positive in skin test. Among the 13 cases who were sensitive to the E.coli type L-Asp, 0 case was sensitive to the PEG-Asp in the first dose and 2 cases were sensitive to the PEG-Asp in the second dose. 2 cases of allergic in Group A fail the second dose chemotherapy, 4 patients were unable to continue chemotherapy after desensitization in Group B.

2.2 coagulation function

The difference in the extension of activated partial thromboplastin time (APTT), the extension of prothrombin time (PT), the reduction of antithrombin Ⅲ (AT-Ⅲ), and the reduction of fibrinogen (FIB) between the two groups weren't significant. D-dimer increased more than three times in 4 cases of Group A, while there were 8 cases for group B. Only 2 cases in group B had clinical manifestations, 1 case showed severe headache, convulsions and visual impairment,1 case showed severe headache and vomiting. (Table 1).

Table 1 The adverse reactions of hemagglutinin's classification

Adverse reactions	APTT (Prolonged)					PT (Prolonged)					FIB (Reduced)					AT-Ⅲ (Reduced)	D-dimer (Rised)
Classification	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	Unclassification	Unclassification
Group A	22	18	0	0	0	38	2	0	0	0	19	6	14	1	0	23	4
Group B	43	17	0	0	0	60	0	0	0	0	26	18	14	2	0	33	8
P	0.133					0.059					0.059					0.967	0.758

2.3 The changes in blood (Table 2)

In Group A (>Level 2) , there were 16 cases of leukopenia，26 cases of neutropenia, 0 case of hypohemoglobinemia，5 cases of thrombocytopenia; While in Group B (>Level 2) , there were 28 cases of Leukopenia，46 cases of Neutropenia, 2 cases of Hypohemoglobinemia，16 cases of Thrombocytopenia.The difference above had no significance.

Table 2 The adverse reactions of hemogram's classification

Adverse reactions	WBC (Reduced)					ANC (Reduced)					Hb (Reduced)					PLT (Reduced)				
Classification	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4	0	1	2	3	4
A group	8	7	9	10	6	7	3	4	12	14	32	6	2	0	0	32	3	3	1	1
B group	10	9	13	16	12	7	3	4	14	32	44	6	7	3	0	39	5	9	4	3
P	0.450					0.080					0.314					0.090				

2.4 Biochemical changes in each index (Table 3)

In this study,there was no case showed the rise of Amylase. Other adverse effect such as the increasion of Glutamate Pyruvate Transaminase, the reduction of Hypoproteinemia, the rise of Bilirubin,the increasion of Blood Urea Nitrogen, the elevation of Blood glucose all had a lower incidence rate. what is more, the differences of the adverse effect above between the two group had no significance.

Table 3 Comparison of biochemical index

Grouping	Amylase (increased)	ALT (increased)	Hypoproteinemia	Bilirubin (increased)	Cholesterol (increased)	BUN (increased)	Bood glucose (in (increased)
Agroup	0 (0)	5 (12.5%)	20 (50%)	4 (10%)	2 (5%)	3(7.5%)	0 (0)
Bgroup	0 (0)	5 (8.3%)	29(48.3%)	4(6.7%)	0(0)	3(5%)	3 (5%)
P	1.000	0.734	1.000	0.821	0.307	0.932	0.402

2.5 Other adverse reactions

The number of patients who have Nausea and Vomiting, abdominal pain and diarrhea, ulcers in the Group A was 7 (17.5%), 3 (7.5%), 0 (0), while it was 20 (33.3%), 13 (21.7%), 2 (3.3%) in Group B, there were no statistical significance.

2.6 Curative effect and Length of stay

Both before and after chemotherapy, bone marrow examination showed complete remission, Recent follow-up showed complete remission, Long-term sustained remission time need to continue follow-up. The average hospital stay of Group A was 11.5 ± 7.1 days, while which was 18.5 ± 4.9 days for Group B, $P < 0.05$ was statistically significant.

3 Discussion

L-ASP is one kind of enzyme inhibitor, meantime has the property of allogeneic macromolecular proteins[4]. It can hydrolyze asparagine enzyme to hinder the synthesis of the protein and inhibit the proliferation of cells when affecting the leukemic cells. When roling in normal cells it leads to lots of adverse reactions, so different dosage forms of L-Asp was developed and applied in order to reduce the adverse reactions and improve curative effect. E. coli-type is variant protein extracted from E. coli culture fluid, which half life is about 20 hours, needing repeated intravenous injection to achieve sufficient drug concentration, the high immunogenicity can stimulate the body to produce specific antibodies causing allergic reactions, and with the increasing of drug use frequency , the incidence of allergy increased, reaching to 30% -75%, at the same time the presence of antibodies makes the L -ASP activity decreased greatly and reduces the curative effect. Pegaspargase is the polyethylene glycol (PEG) conjugation of L-asparaginase, reducing the potential immunogenicity (reduced 99%) meanwhile maintaining its activity [5]. Compared with the E. coli dosage form, PEG-Asp reduces antibody formation, significantly prolonges drug action time, extends half-life to 5.5 days, reduces medication frequency, and decreases the incidence of allergic reactions. A test showed that PEG-Asp can improve and prolong the activity of L-Asp, reduce the incidence of high titer antibodies and can removed leukemia cells from the bone marrow quickly, to achieve better curative effect.

In this study, 4 patients in Group B showed serious allergic reactions such as laryngeal edema, systemic rash, persistent diarrhea (reaching 6.7%), this higher incidence suggests insecurity in the process of drug use, even if the skin test was negative, health care workers are still required to observe closely. Medication was discontinued and corticosteroids, antihistamines, promethazine and oxygen was added, After these,the allergy symptoms were under control. In Group A 2 cases are sensitive to both PEG-Asp and E. coli L-Asp. While in Group B, 13 cases showed hypersensitivity in E. coli L-Asp, among the 13 cases 11 cases can still complete the chemotherapy of L-Asp through using PEG-Asp, which indicated that there were no cross-immunity between PEG-Asp and L-Asp,so the former can be used as a substitute when the latter brings about allergy. L-Asp inhibits the proliferation of leukemia cells and protein synthesis in normal cells [7-8]. In this study, the incidence of hypoproteinemia was nearly 50%, and edema, circulatiory disorders and opportunistic infections were easy to merge when the patients are in the condition of hypoproteinemia. Most of these patients were complicated with coagulation disorder, no significant correlation adverse reactions came out after plasma protein and coagulation factor was supplemented. Damagment of liver function, decreasing of synthesis of blood coagulation factors in liver induces coagulation disorder such as bleeding[6,9]. Someone reported L-asparaginase could also influence the synthesis of protein C and protein S, which would promote arterial and venous thrombosis [10]. Andrew reported that the thrombosis rate in the ALL children who had received the chemotherapy of L-Asp was 1.1% ~ 14.6%, only 5% had symptoms (most occurred in the central nervous system) [11]. This study found that both groups have different degrees of coagulation disorder, in which 2 patients in Group B had clinical manifestations - severe headache, vomiting, convulsion and visual disturbances. We owe it to thrombosis and bleeding. The high incidence of coagulopathy disorder affects the

safety of medication obviously.The patients who had abnormal blood coagulation can continue the chemotherapy by infusing cryoprecipitate, plasma, vitamin K1,with no deaths. So the clotting function should be monitored dynamicly in the clinical treatment and we should correct the coagulation disorder actively, stop medicating when necessary to avoid bleeding.

L-Asp plays a part in leukemia cells but has little effect on normal cells, so there were no significant mucosal and hematological toxicity [12]. Clinical trials also showed that the PEG-Asp manifests anticancer activity on the tumor of drug-resistance, and we find no polymer-related toxicity [5], so the two groups' neutrophils decreasing has something to do with pirarubicin in the combination chemotherapy. But its relationship with the L-ASP need further research. 2 cases in the Group 1 have increased blood glucose, one case can be controled by stopping the prednisone and plusing insulin, the others can be controled just by adjusting diet. This change was considered as prednisone's side effect. It was also reported that it was related with insulin secretion of the injured pancreas [13]. The children in Group A showed no abnormalities in blood glucose, which was considered to be related with no drug administration on time outside the hospital.

The VDLP and VDPAP project are all strong chemotherapy for patients, all of them were without recurrence during follow-up. Some study compared the 3 year's disease free survival and the 5 year's disease free survival, there were no significant difference between the E-coli type and PEG-Asp[14]. So the two dosage forms had similar inducer remission rates and 3 or 5-year event-free survival[15].

In summary, the difference of allergic reactions' incidence and influence to the blood coagulation function between two dosage form was significant, but the differences in long-term prognosis needs further experimental proof. Douglas SH [16] reported that intensive treatment of PEG-Asp can produce high serum enzyme activity in order to remove the asparagine in serum and cerebrospinal fluid effectively, even if they had used the E. coli-or PEG-Asp,the hypersensitivity toxicity of PEG-Asp is rare and other adverse reactions are rare. L-Asp is the key drug in ALL combination chemotherapy, because of the high rate of allergy we should suspend or terminate chemotherapy when using the E.coli type , which affect the long-term prognosis ultimately, PEG-Asp overcomes this fault,decreases immunogenicity, reduces the generation of antibody to increase the curative effect，improves the prognosis and also has the advantages of less frequency of usage、convenient usage、fewer allergic reactions and short hospital time,which deserves further promotion.

References

[1] Gu LJ. (The third draft revision)[J]. Chinese Journal of P6diatrics, 2006, 44(5):392-395

[2] Yu SY, Hu GQ, Yuan XL. Oncology Clinical. Bei Jing, Science Publishing Company, 2006:566-567

[3] Liu HJ, Wang NL, Li C, et al. L-asparaginase's desensitization treatment of children in acute lymphoblastic leukemia [J]. Journal of Clinical Pediatrics, 2008.26 (2): 91-91,123

[4] Wacker P, Land VJ, Camitta BM, et al. Allergic Reactions to E. coli L-Asparaglnase Do Not Affect Outcome in Childhood B-precursor Acute Lymphoblastic Leukemia：A Children's Oncology Group Study [J]. J Pediatr Hematol Oncol, 2007, 29(9):627-632

[5] Sun XF, Xu QM, Ao GZ, et al. Antitumor agents: multidrug resistance and enhanced permeability and retention [J]. Chinese Journal of New Drugs, 2007.16(1):16-20

[6] Bodmer M, Sulz M, Stadlmann S, et a1. Fatal liver failure in an adult patient with acute lymphoblastic leukemia following treatment with L-asparaginase [J]. digestion, 2006,74(1) ：28-32

[7] Aoki CA, Bowlus CL, RossaroL. An adult case 0f acute lymphoblastic leukaemia presenting as hepatic dysfunction [J]. Dig Liver Dis, 2005,37(3):206-210

[8] Zakarija A, Kwaan HC. Adverse effects on hemostatic function of drugs used in hematologic malignancies [J]. Semin Thromb Hemost, 2007, 33(4) ：355-364

[9] Hongo T, Okada S, Ohzeki T, et a1. Low plasma levels of hemo-static proteins during the induction phase in children with acute lymphoblastic leukemia：a retrospective study by the JACLS Japan Association of Childhood Leukemia Study [J]. Pediatr Int, 2002, 44(3): 293-299

[10] Murakawa M. Okamura T, Shibuya T, et al. Use of a synthetic protease inhibitor for the treatment of L-asparaginase-induced acute pancreatitis complicated by disseminated intravascular coagulation [J]. Ann Hematol, 1992, 64(5):249-252

[11] Andrew M, Brooker L, Mitchell L. Acquired antithrombin Ⅲ deficiency secondary to asparaginase therapy in childhood acute lymphblastic leukaemia[J]. Blood Coagul Fibrinol, 1994, 5:524-526

[12] Guo M, Xue H, Li CY, et al. VAD-ASP project in the therapy of reccured and refractory adult acute lymphocytic leukemia [J]. Medical Research and Education, 2009,26(5):24-25

[13] Alves C, Chaves C, Souza M. Transient diabetes mellitus related to L-asparaginase therapy [J]. Arq Bras Endocrinol Metabo1, 2007, 51 (4) ：635-638

[14] Liu F, Zou Y, Zhang L, et al. Long-term efficacy of polyethylene glycol conjugated asparaginase(PEG-Asp) in newly diagnosed childhood acute lymphoblastic leukemia (ALL) [J]. Journal of China Pediatric Blood and Cancer, 2010,15 (6) :254-256

[15] Avramis VI, Sencer S, Periclou AP, et al. A randomized comparison of native Escherichia coli asparaginase and polyethylene glycol conjugated asparaginase for treatment of children with newly diagnosed standard-risk acute lymphoblastic leukemia: a Children's Cancer Group study[J]. Blood, 2002, 99:1986-1994

[16] Douglas SH, Julie RP, Blythe GT, et al. Asparaginase Pharmacoki-

netics After Intensive Polyethylene Glycol-Conjugated L-Asparaginase Therapy for Children with Relapsed Acute Lymphoblastic Leukemia[J]. Clinical Cancer Research, 2004, 10:5335-5341

培门冬酶治疗儿童急性淋巴细胞性白血病的不良反应观察

王 岳 李学荣△ 仲 任 杨 静 孙立荣

(青岛大学医学院小儿血液科 山东 青岛 276003)

摘要 目的:观察左旋门冬酰胺酶两种常用剂型在急性淋巴细胞性白血病患儿联合化疗中的治疗反应。方法:本院2010.3-2010.12行长春新碱+吡柔比星+门冬酰胺酶+强的松方案化疗的急性淋巴细胞白血病患儿,使用含有聚乙二醇化的左旋门冬酰胺酶剂型培门冬酶即VDPAP者作为A组(40例)与既往使用含大肠杆菌剂型即VDLP者B组(60例)对比,观察不良反应。化疗前后检测血象,肝功能,凝血功能,观察过敏情况等,记录化疗后第28天的各项指标。结果:A组过敏发生2例(5%)而B组过敏发生13例(21.67%),P值0.045,有统计学意义。既往对大肠杆菌剂型发生过敏的13例患儿首剂使用PEG-Asp均无过敏,2例于第二剂时出现皮试阳性。A组(>2级)白细胞减少16例,中性粒细胞减少26例,血红蛋白降低0例,血小板减少5例,纤维蛋白原降低1例,部分凝血活酶时间延长0例;B组(>2级)白细胞减少28例,中性粒细胞减少46例,血红蛋白降低2例,血小板减少16例,纤维蛋白原降低2例,部分凝血活酶时间延长0例。A组(未分级)抗凝血酶III降低23例,D二聚体升高4例,谷丙转氨酶升高5例;B组(未分级)抗凝血酶III降低33例,D二聚体升高8例,谷丙转氨酶升高5例。.血液学不良反应差异无统计学意义。A组平均住院日11.14天。B组平均住院日18.47天。结论:左旋门冬酰胺酶两种剂型不良反应相当,但培门冬酶具有使用次数少,使用方便,过敏率低,缩短住院日的优点。

关键词 培门冬酶;急性淋巴细胞白血病;大肠杆菌型;左旋门冬酰胺酶;不良反应

中图分类号:R725.5,R733.7 **文献标识码**:A **文章编号**:1673-6273(2011)14-2691-05

作者简介:王岳,女,硕士,主要研究方向:小儿血液与肿瘤,

Tel: 13296391778, E-mail: gumenghuangshu@163.com

△通讯作者:李学荣,电话:0532-82911313

(收稿日期:2011-01-27 接受日期:2011-02-23)