Perspective

Consideration of Glucocorticoids and *Escherichia coli*-derived L-asparaginase in the treatment of pediatric acute lymphoblastic leukemia

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Glucocorticoids (GCs) are steroid hormones these are synthesized in the adrenal cortex. After binding to the nuclear glucocorticoid receptor (GR), activated GR complexes play a major role in immune system regulation by exerting a variety of effects such as inhibition of cyclooxygenase and inflammatory cytokines (IL-1, IL-2, IL-5, IL-6, INF-γ) synthesis, neutrophil induction, lymphocyte activation, etc. (1). Consequently, GCs are used to treat inflammation associated with autoimmune diseases, sepsis, asthma and allergies. In addition, GCs also have the ability to induce apoptosis (2). GR complexes engage the pro-survival and pro-apoptotic factors at the mitochondrial level. As a result, caspases and endonuclease are activated for induced apoptosis. Recent studies have clarified many aspects of the apoptotic pathway, including the activation of the caspases and multicatalytic proteasomes and suppression of pro-survival transcription factors such as AP-1, c-myc, nuclear factor-κB and Bcl-2 family members (3).

GCs are key drugs in the treatment of acute lymphoblastic leukemia (ALL), the most common pediatric malignancy, where they have been used for remission induction and intensification therapy in children and adolescents for decades (4,5). There are several types of GCs, such as hydrocortisone, prednisone (PSL), prednisolone, methylprednisolone, dexamethasone (DEX), betamethasone, etc. Each has a difference of pharmacological effect to the target cells. Whether DEX can be used as an alternative to PSL is very important topic of discussion. Some reports have described the advantages of DEX over PSL. DEX is associated with a decreased incidence of meningeal leukemia due to enhanced CSF penetration (6), and in comparison with PSL, DEX is five to six fold more effective in including lymphoblast apoptosis *in vitro*. Some authors have described the advantages of DEX over PSL in a clinical (7). However conclusion did not come out. One meta-analysis suggested that DEX is more efficacious than PSL in remission induction phase depending on the administered dose (8). However, DEX is also associated with more toxicity and increases the risk of osteonecrosis and infection.

Asparagine is an amino acid for required to the synthesis of protein and lymphoblast require a large amount of this amino acid to fuel their growth and synthetic demands. L-Asparaginase (L-Asp) isolated from *Escherichia coli (E. Coli)* inhibits the growth of lymphoblastic leukemia cells and it is an important chemotherapeutic agent for pediatric ALL and contributes to improvement of event-free survival (EFS). However, many adverse effects of L-Asp have been reported (9), most commonly liver dysfunction, diarrhea, vomiting, pancreatitis, low serum levels of antithrombin III and fibrinogen, mild bone marrow suppression and hypersensitivity (10). Allergic responses with repetitive L-Asp use can occur in 6% to 43% of cases (11), because a patient's immune system recognizes *E. coli*-derived L-Asp as a foreign entity.

Recently, one paper described very noteworthy results (12). They compared the efficacy of DEX with PSL in intensification phase. Patients were administered PSL in the remission induction phase, and randomly assigned to receive either DEX or PSL in the intensification phase and continuation phases. Further, dosing regimens were individualized by monitoring nadir serum asparaginase activity (NSSA) and adjusting the dose of *E. coli*-derived

L-Asp to maintain a therapeutic level. They found that DEX and individualized L-Asp dosing were both independent predictors of favorable EFS, without any indication of interaction in their proportional hazard regression modeling. In comparison with PSL administration, DEX administration improved the 5-year EFS. Although, DEX was associated with a higher risk of infection during post-induction treatment, particularly in adolescents, death rate due to toxicity remained unaffected. The cumulative dose of neither of the GCs affected the rate of osteonecrosis in less than 10 years of age. The improvement in 5-year EFS due to individualized dosing of L-Asp. This result suggested that silent inactivation was prospectively identified on the individualized dosing but not the fixed dosing. Although individualized dosing was expected to avoid overdosing and reduce the incidence of adverse effects, it did not reduce L-Asp-associated toxicity.

In conclusion, the selection of DEX and PSL for pediatric ALL treatment should be carefully considered. Previous studies have described the advantages and disadvantages of DEX over PSL (13). In comparison with PSL, DEX is expected to improve disease prognosis when used in both remission induction and intensification phases (8). Further, DEX may be beneficial for pediatric ALL patients when used in conjunction with the proper prophylaxis against infection and osteoporosis, especially for older children and adolescents. Patient age should also be considered when selecting DEX or PSL. Similarly, the administration and dosing method should be considered when using L-Asp. Even though L-Asp markedly improves prognosis, it should be avoided in pediatric ALL patients considering the high frequency of severe L-Asp associated hypersensitivity (11). A complex of polyethylene glycol (PEG) conjugated with L-Asp is approved for the treatment of pediatric ALL in some countries. PEG-L-Asp has a longer half-life, equivalent efficacy and less immunogenicity than native L-Asp (14). Consequently, if PEG-L-Asp is substituted for native L-Asp in the same protocol, individualized dosing of PEG-L-Aps may in fact reduce toxicity whilst maintain the therapeutic effect.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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