# 소아 면역혈소판감소자색반병 환자에서 고용량 덱사메타손 요법의 효과

이현옥[1] · 장성환[1] · 백희조[1] · 김호성[1] · 박수민[1] · 신명근[2] · 국 훈[1]

전남대학교 의과대학 화순전남대학교병원 [1]소아과학교실, [2]진단검사의학과교실

# The Efficacy of High Dose Dexamethasone Therapy in Children with Immune Thrombocytopenic Purpura

Hyun Ok Lee, M.D.[1], Seong Hwan Chang, M.D.[1], Hee Jo Baek, M.D., Ph.D.[1], Ho Sung Kim, M.D.[1], Su Min Park, M.D.[1], Myung Geun Shin, M.D.[2] and Hoon Kook, M.D.[1]

*Departments of [1]Pediatrics and [2]Laboratory Medicine, Chonnam National University Hwasun Hospital, Chonnam National University Medical School, Hwasun, Korea*

**Background:** Few studies of high dose dexamethasone (HD-DXM) therapy in children with immune thrombocytopenic purpura (ITP) have been reported. The purpose of this study is to investigate efficacy and safety of repeated HD-DXM therapy as second-line treatment of ITP in childhood.

**Methods:** We retrospectively analyzed the medical records of patients <18 years of age with primary ITP who received more than 2 cycles of HD-DXM therapy from May 2004 to January 2018. HD-DXM was given orally in 4-day pulses every 28 days as a 20-40 mg/1.73 $m^2$ daily dose.

**Results:** A total of 26 patients (male, 19; female, 7) were enrolled and their median age was 6 years (range, 1-15). All patients had received previous treatment for ITP. A median 6 cycles (range, 2-19) of HD-DXM was given. On the beginning of HD-DXM therapy, three patients satisfied the criteria for newly diagnosed ITP, 16 for persistent ITP and 7 for chronic ITP. Relapse-free survival (RFS) of responders (n=9) after the last HD-DXM cycle was estimated to be 38.1±17.2%, lasting for a median 9.1 months (range, 5.6-46.2). According to response after the 2nd cycle, RFS of responders (n=13) was significantly higher than non-responders (23.1±11.7% vs. 7.7%±7.4%, $P$=0.001). The most common adverse event was irritability (30.8%), followed by fatigue (19.2%).

**Conclusion:** HD-DXM therapy in children was relatively tolerated and response after therapy was acceptable. More courses of HD-DXM may be feasible in responders after two cycles of HD-DXM.

**Key Words:** Immune thrombocytopenic purpura, High dose dexamethasone

pISSN 2233-5250 / eISSN 2233-4580
https://doi.org/10.15264/cpho.2018.25.2.102
Clin Pediatr Hematol Oncol 2018;25:102～107

Received on September 24, 2018
Revised on September 26, 2018
Accepted on October 10, 2018

**Corresponding Author:** Hee Jo Baek
Department of Pediatrics, Chonnam National University Hwasun Hospital, Chonnam National University Medical School, 322 Seoyang-ro, Hwasun-eup, Hwasun 58128, Korea
Tel: +82-61-379-7695
Fax: +82-61-379-7697
E-mail: swan93@naver.com
ORCID ID: orcid.org/0000-0003-3830-8134

## Introduction

Immune thrombocytopenic purpura (ITP) is an autoimmune disorder characterized by low platelet counts due to immunologic destruction of normal platelets and suboptimal platelet production. ITP is one of the most common acquired bleeding disorders in children. ITP during

childhood is usually a short self-limiting disorder without any late sequelae. Approximately 80% of children diagnosed with ITP recover within 6-12 months of diagnosis. However, 20-25% of children with newly diagnosed ITP ultimately developed chronic ITP, defined as persistent thrombocytopenia lasting for more than 12 months [1].

For pediatric patients with newly diagnosed ITP requiring treatment, intravenous immunoglobulin (IVIg), anti-D immunoglobulin (anti-D), or short course of corticosteroid is used as first-line treatment. High-dose dexamethasone (HD-DXM) therapy may be considered for newly diagnosed ITP unresponsive to initial treatment and with persistent or chronic ITP in children [2-4]. Few studies of HD-DXM therapy in children with ITP have been reported [5-11].

The purpose of this study is to investigate efficacy and safety of repeated HD-DXM therapy as second-line treatment of ITP in childhood.

## Materials and Methods

### 1) Patients

We retrospectively analyzed the medical records of patients <18 years of age with primary ITP who received at least 2 cycles of HD-DXM therapy at Chonnam National University Hwasun Hospital from May, 2004 to January, 2018. HD-DXM was used as second-line treatment for children with ITP who had a platelet count of no more than $20\times10^9$/L despite treatment with IVIg, anti-D, or conventional doses of corticosteroid. Study protocols were approved by the Institutional Review Boards of Chonnam National University Hwasun Hospital.

Diagnosis of ITP was based on commonly adopted criteria: patient's medical history, Physical examination, complete blood count, and peripheral blood smear. Prior to treatment with steroid, bone marrow aspirate was performed on most of patients. Antinucleus antibody was also performed on all enrolled patients and one patient showed positivity of autoimmune markers.

Primary ITP was defined as a platelet count $<100\times10^9$/L in the absence of other causes or disorders that may be associated with thrombocytopenia [2]. We also classified ITP as newly diagnosed (diagnosis to 3 months), persistent (3 to 12 months from diagnosis), or chronic (lasting for more than 12 months) according to the criteria of the ITP International working group [13].

### 2) Therapy schedule

HD-DXM of 10-40 mg/1.73 $m^2$ daily was given orally for 4 consecutive days every 28 days for at least 2 cycles. All patients were treated on an outpatient basis. If platelet count remained no more than $20\times10^9$/L between courses or bleeding symptoms related to thrombocytopenia were present, other therapies such as IVIg or anti-D were given.

### 3) Response evaluation

The response was evaluated according to the American Society of hematology 2011 evidence-based guideline [2]; 1) complete response (CR), defined as platelet count $\geq100\times10^9$/L measured on 2 occasions >7 days apart and the absence of bleeding; 2) response (R), defined as platelet count $\geq30\times10^9$/L and a greater than 2-fold increase in platelet count from baseline measured on 2 occasions >7 days apart and the absence of bleeding; 3) no response (NR), defined as platelet $<30\times10^9$/L or a less than 2-fold increase in platelet count from baseline or the presence of bleeding on occasions more than a day apart.

Complete blood counts were obtained at the beginning of each cycle and at 7 days or 14 days after each cycle and every 14 days or 28 days after the last cycle.

Relapse was defined as a platelet count decrease less than or equal to $30\times10^9$/L or the presence of bleeding symptoms due to thrombocytopenia after the achievement of initial response [2].

Relapse-free survival (RFS) was defined as the time interval between achievement of response and relapse [11].

After the 2nd cycle of HD-DXM therapy and at one month after the last cycle, CBC and a physical examination was performed. Adverse effects were investigated for each cycle, as reported by the patient or by the parents. Long-term response was evaluated at 1 year after the last cycle of HD-DXM therapy in responder patients.

According to response of therapy, they were divided into 2 groups; responder if CR and R and non-responder if NR.

### 4) Statistical analysis

Data were analyzed using IBM SPSS vers.21 (IBM Co., Armonk, NY, USA). Relapse-free survival was measured from the date of response achievement to the date of relapse. The multivariate analysis of RFS was done using the Cox proportional hazard model. The probability of RFS was calculated using the Kaplan-Meier method. Statistically significant *P* values were less than or equal to 0.05.

## Results

### 1) Patients characteristics

A total of 26 patients (male, 19; female, 7) were enrolled in the study (Table 1), with median platelet count of $15\times10^9$/L (range, $<2\text{-}33\times10^9$) and bleeding symptoms (skin purpura or petechia, N=9; epistaxis or oral mucosa bleeding, N=5) within 3 months before entering the study. The median age was 6 years (range, 1-15) and patients with more than 10 years were 9 (34.6%). All patients had received previous treatments with immune globulin and prednisolone.

**Table 1.** Characteristics of the enrolled patients

| Characteristic | Total |
|---|---|
| Patients, N | 26 |
| Male/female, N | 19/7 |
| Median age, years (range) | 6 (1-15) |
| 1-9 years, N | 17 |
| ≥10 years, N | 9 |
| Median platelet count, $\times10^9$/L (range) | 15 (<2-33) |
| Bleeding severity | |
| None | 12 |
| Mild[a] | 9 |
| Moderate[b] | 5 |
| Previous treatments | |
| IVIg | 26 (100%) |
| Prednisolone | 26 (100%) |
| Anti-D immune globulin | 13 (50%) |
| Methylprednisolone | 4 (15.4%) |
| Cyclosporine | 2 (7.7%) |
| Vincristine | 2 (7.7%) |

[a]Defined as skin manifestations only, such as bruising and petechia.
[b]Defined as mucosal bleeding, such as epistaxis and gingival bleeding.
IVIg, intravenous immunoglobulin.

At the beginning of HD-DXM therapy, 3 patients satisfied the criteria for newly diagnosed ITP, 16 for persistent ITP and 7 for chronic ITP. All of them progressed into chronic ITP later. The median follow-up period of 26 patients was 51 months (range, 12-148).

Median 6 cycles (range, 2-19) of HD-DXM was given and 15 patients (57.7%) completed at least 6 cycles. Treatment was stopped before the 6th cycle of HD-DXM in 11 patients (42.3%) due to no response (N=7), medical decision (N=2, CR after completion of the 4th cycle) and adverse events (N=2; irritability and fatigue).

Splenectomy was performed in 7 patients (Fig. 1). All of them were persistent ITP at the start of HD-DXM therapy and did not respond to HD-DXM therapy.

### 2) Response to high dose-dexamethasone therapy

Fig. 1 demonstrated the response for patients treated with HD-DXM according to ITP type (Fig. 1).

After the 2nd cycle of HD-DXM, 13 patients showed response (R, N=13; CR, N=0). According to response after the 2nd cycle of HD-DXM, probability of RFS of responders (N=13) was significantly higher than that of non-responders (N=13) (23.1±11.7% vs. 7.7±7.4%, *P*=0.001; Fig. 2A).

Response rate after the last cycle of HD-DXM was 34.6% (9/26). Among responders after the last cycle, 8 patients showed response after the 2nd cycle of HD-DXM. All 3 patients with newly diagnosed ITP on beginning of HD-DXM therapy showed no response. Among 16 patients with persistent ITP, 5 patients showed response (response rate, 31.2%; R, N=2; CR, N=3) and 4 of 7 patients with chronic ITP patients showed response (response rate, 57.1%; R, N=3; CR, N=1). No statistically significant difference of RFS by ITP type was found (newly diagnosed vs. persistent vs. chronic, 0% vs. 12.5% vs. 19.0%, *P*=0.258). In the responders (CR+R, N=9) after the last cycle, median platelet count was $100\times10^9$/L (range, $35\text{-}426\times10^9$/L) and in non-responders, the median platelet count was $17\times10^9$/L (range, $<2\text{-}30\times10^9$/L). RFS of responders (N=9) after the last cycle of HD-DXM was estimated to be 38.1±17.2% (Fig. 2B), lasting for a median of 9.1 months (range, 5.6-46.2). RFS of non-responders (N=17) was estimated to

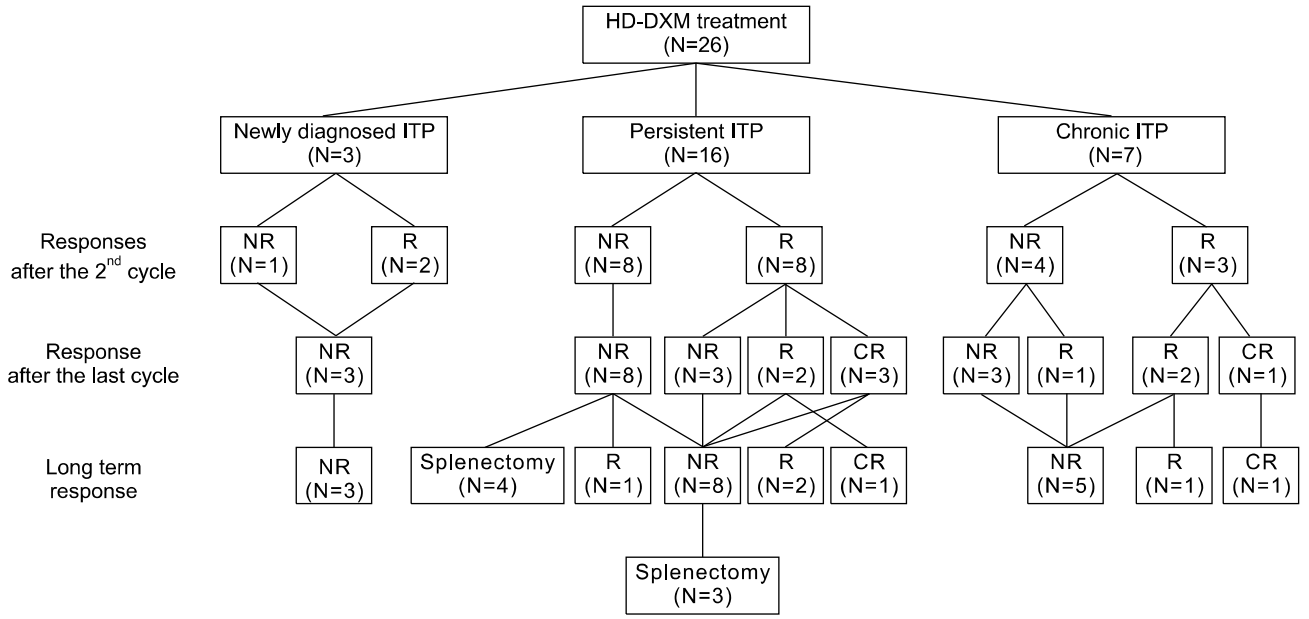


**Fig. 1.** Response to high dose dexamethasone therapy in a total 26 patients with immune thrombocytopenic purpura. CR, complete response (platelet count $\geq 100\times10^9$/L measured on 2 occasions $>7$ days apart); R, response (platelet count $\geq 30\times10^9$/L and a greater than 2-fold increase in platelet count from baseline measured on 2 occasions $>7$ days apart); NR, no response.

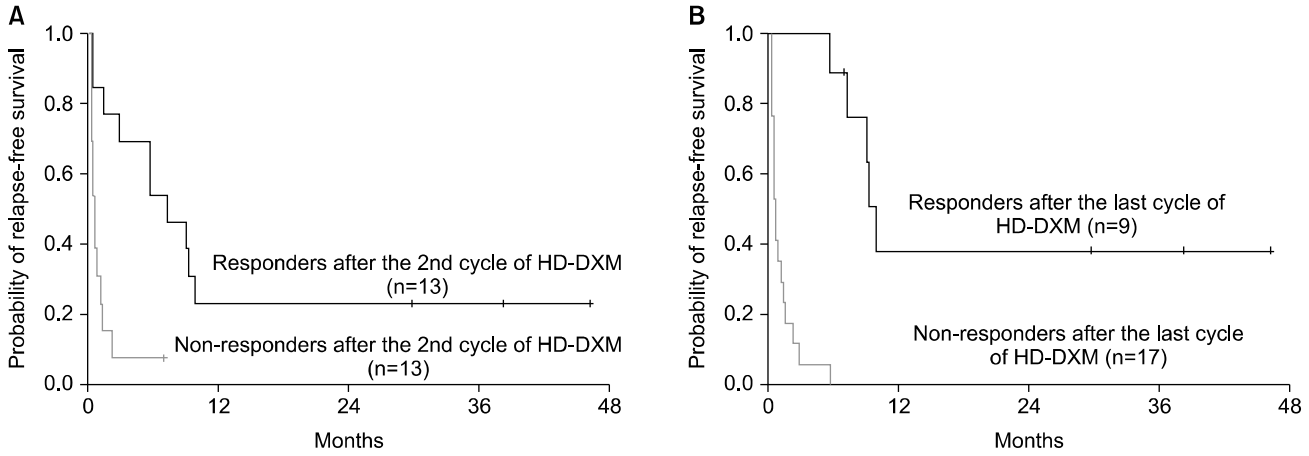


**Fig. 2.** (A) Relapse-free survival according to response after the 2nd cycle of high dose dexamethasone (HD-DXM). (B) Relapse-free survival according to response after the last cycle of HD-DXM.

be 0%.

Long-term responses were observed in 6 of 9 responder patients after the last cycle of HD-DXM; that is, 6 of 26 patients (23%). In particularly, CR was found in 2 (33.3%) and R in 4 (15.4%) of 9 patients. Median platelet count at last control was $90.5\times10^9$/L (range, 45-$192\times10^9$/L).

In multivariate analysis of RFS, responders after the 2nd cycle of HD-DXM and chronic ITP on the beginning of HD-DXM were significantly independent factors for RFS ($P<0.005$, $P<0.004$, respectively) (Table 2).

### 3) Adverse events

Various adverse events were observed in 20 of 26 patients (76.9%) (Table 3). The most common adverse event was irritability (30.8%), followed by fatigue (19.2%), facial flushing, pruritus and increased appetite. Most of them

**Table 2.** Multivariate analysis for relapse-free survival

| | Hazard ratio (95% CI) | *P*-value |
|---|---|---|
| Male vs. female | 1.277 (0.309-5.273) | 0.736 |
| Age <10 years vs. >10 years | 1.162 (0.293-4.607) | 0.831 |
| Non-responders vs. responders after 2nd cycle of HD-DXM | 0.083 (0.022-0.32) | <0.005 |
| ITP type | | |
| Newly diagnosed | 1 | |
| Persistent | 0.269 (0.006-1.099) | 0.068 |
| Chronic | 0.08 (0.014-0.456) | 0.004 |

CI, confidence interval; HD-DXM, high dose-dexamethasone; ITP, immune thrombocytopenic purpura.

**Table 3.** Adverse effects of high dose dexamethasone therapy

| Symptoms | N (%) |
|---|---|
| Irritability | 8 (30.8) |
| Fatigue | 5 (19.2) |
| Facial flushing | 4 (15.4) |
| Pruritus | 4 (15.4) |
| Increased appetite | 4 (15.4) |
| Moodiness | 2 (7.7) |
| Myalgia | 2 (7.7) |
| Skin eruption | 2 (7.7) |
| Abdominal pain | 2 (7.7) |
| Loss of appetite | 1 (3.8) |
| Sensation of bloating | 1 (3.8) |
| Nausea | 1 (3.8) |
| Headache | 1 (3.8) |

(N=15) appeared after first cycle of HD-DXM therapy. In 2 patients, treatment with HD-DXM had to be discontinued due to irritability and fatigue at the end of 4th cycles and 5th cycle, respectively. During therapy cycles, there were no bleeding complications.

## Discussion

Several similar regimens of HD-DXM [5-11] have been used with varying success in both children and adults with chronic ITP since the report by Andersen in 1994. Andersen *et al.* [12] reported a 100% response rate in 10 adult patients treated with pulsed HD-DXM for chronic ITP. Most of studies of HD-DXM therapy in children and adolescents were small which included 25 or less patients with chronic or persistent ITP [5-11].

Kühne *et al.* [6] examined the response to HD-DXM (40 mg/d×surface area of the child divided by 1.8 $m^2$ for 4 consecutive days, every 4 weeks for six cycles) administered orally to 11 children with chronic ITP. They found excellent short-term responses (increasing to platelet $>100\times10^9$/L within 3 days of completion of the first HD-DXM cycle), but the therapy induced long-term response in fewer than half of the children. Borgna-Pignatti *et al.* [7] performed a similar study on 17 children with HD-DXM at a dosage of 40 mg/$m^2$ for 4 consecutive days every 4 weeks for six cycles. They found that 35% of the patients had platelet counts within normal range at 1 month after completion of the sixth cycles. One year later, 29% of the patients still had normal platelet values. Chen *et al.* [8] treated 7 children with pulsed HD-DXM (40 mg/$m^2$/day for 4 consecutive days, every 4 weeks). At the end of the sixth cycle, three patients (43%) had response (platelet count $\geq50\times10^9$/L), but only one patient had a platelet count of more than $50\times10^9$/L at 1 year after completion of therapy.

In a prospective, randomized trial [5] which was investigated whether pulsed HD-DXM (0.6 mg/kg/d for 4 days every 4 weeks for 6 months) is more efficacious than IVIg (800 mg/kg once monthly for 6 months) as treatment of symptomatic chronic ITP in childhood, 12 patients received HD-DXM. A short-term response (platelet count $30\times10^9$/L on day 3 of the first treatment cycle) of HD-DXM is 75%, but long-term partial or complete response occurred in 25% of treated patients.

In this study, response rate is comparable to those of other studies. Response rate after the last cycle of HD-DXM was 34.6% (9/26) and long-term response occurred in 6 of 26 patients (23%). RFS of responders (N=9) after the last cycle of HD-DXM was estimated to be 38.1±17.2% lasting

for a median 9.1 months (range, 5.6-46.2).

Another study [9] reported the results of pulses of HD-DXM for previously untreated children with newly diagnosed ITP. HD-DXM was given as a daily dose of 20 mg/m$^2$ for 4 days, every 14 days for 4 cycles. Their response rate was 85.7% and RFS at 15 months was 96%. However, in our study, all 3 patients with newly diagnosed ITP on the beginning of HD-DXM therapy showed no response.

In this study, treatment with HD-DXM was well tolerated. We observed adverse events in 20 of 26 patients (76.9%). However, only 2 patients discontinued the treatment for adverse events related to therapy. Most of them appeared after first cycle of HD-DXM therapy.

Our study showed responders after the 2$^{nd}$ cycle of HD-DXM had significantly higher response rate than non-responders (23.1±11.7% vs. 7.7±7.4%, $P$=0.001). Most of patients with long-term response (5/6) showed response after the 2$^{nd}$ cycle of HD-DXM. On the multivariate analysis the response after the 2$^{nd}$ cycle of HD-DXM and chronic ITP on the beginning of HD-DXM were independent factors influencing the RFS ($P$<0.005, $P$<0.004, respectively). Therefore, repeated HD-DXM therapy of more than 2 cycles could be administered in responders after the 2$^{nd}$ cycle of HD-DXM.

In conclusion, HD-DXM therapy in children was relatively tolerated and response after therapy was acceptable. More repeated HD-DXM may be feasible for selected children with ITP, such as responders after 2$^{nd}$ cycles of HD-DXM with chronic ITP. Larger trials are warranted to clarify the clinical effectiveness of pulsed HD-DXM treatment and to identify the children with ITP who will benefit the most from this type of therapy.

## References


1. Nomura S. Advances in diagnosis and treatments for immune thrombocytopenia. Clin Med Insights Blood Disord 2016;9:15-22.
2. Neunert C, Lim W, Crowther M, et al. The American Society of Hematology 2011 evidence-based practice guideline for immune thrombocytopenia. Blood 2011;117:4190-207.
3. Jang JH, Kim JY, Mun YC, et al. Management of immune thrombocytopenia: Korean experts recommendation in 2017. Blood Res 2017;52:254-63.
4. Cuker A, Neunert CE. How I treat refractory immune thrombocytopenia. Blood 2016;128:1547-54.
5. Hedlund-Treutiger I, Henter JI, Elinder G. Randomized study of IVIg and high-dose dexamethasone therapy for children with chronic idiopathic thrombocytopenic purpura. J Pediatr Hematol Oncol 2003;25:139-44.
6. Kühne T, Freedman J, Semple JW, Doyle J, Butchart S, Blanchette VS. Platelet and immune responses to oral cyclic dexamethasone therapy in childhood chronic immune thrombocytopenic purpura. J Pediatr 1997;130:17-24.
7. Borgna-Pignatti C, Rugolotto S, Nobili B, et al. A trial of high-dose dexamethasone therapy for chronic idiopathic thrombocytopenic purpura in childhood. J Pediatr 1997;130:13-6.
8. Chen JS, Wu JM, Chen YJ, Yeh TF. Pulsed high-dose dexamethasone therapy in children with chronic idiopathic thrombocytopenic purpura. J Pediatr Hematol Oncol 1997;19:526-9.
9. Mazzucconi MG, Fazi P, Bernasconi S, et al. Therapy with high-dose dexamethasone (HD-DXM) in previously untreated patients affected by idiopathic thrombocytopenic purpura: a GIMEMA experience. Blood 2007;109:1401-7.
10. Adams DM, Kinney TR, O'Branski-Rupp E, Ware RE. High-dose oral dexamethasone therapy for chronic childhood idiopathic thrombocytopenic purpura. J Pediatr 1996;128:281-3.
11. Wali YA, Al Lamki Z, Shah W, Zacharia M, Hassan A. Pulsed high-dose dexamethasone therapy in children with chronic idiopathic thrombocytopenic purpura. Pediatr Hematol Oncol 2002;19:329-35.
12. Andersen JC. Response of resistant idiopathic thrombocytopenic purpura to pulsed high-dose dexamethasone therapy. N Engl J Med 1994;330:1560-4.
13. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood 2009;113:2386-93.