THERAPY WITH HIGH-DOSE DEXAMETHASONE (HD-DXM) IN PREVIOUSLY UNTREATED PATIENTS AFFECTED BY IDIOPATHIC THROMBOCYTOPENIC PURPURA.

A GIMEMA EXPERIENCE.

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Running head: HD-DXM in untreated ITP patients

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Abstract

In Idiopathic Thrombocytopenic Purpura (ITP) corticosteroids have been widely recognized as the most appropriate first-line treatment, even if the best therapeutic approach is still a matter of debate. Recently, a single HD-DXM course was administered as first-line therapy in adult ITP patients. In this paper we show the results of two prospective pilot studies (monocentric and a multicentric, respectively) concerning the use of repeated pulses of HD-DXM in untreated ITP patients.

Monocentre study: 37 severe ITP patients, age ≥ 20 and ≤ 65, were enrolled. HD-DXM, in 4 day pulses, every 28 days, for 6 cycles was given. Response rate was 89.2%; relapse free survival (RFS) 90% at 15 months; long-term responses, lasting for a median time of 26 months (6-77), were 25/37 (67.6%).

Multicentre study: 95 severe ITP patients, age ≥ 2 and ≤ 70, were enrolled. HD-DXM in 4 days pulses, every 14 days, for 4 cycles was given, 90 completed 4 cycles. Response rate (85.6%) was similar in patients classified by age (<18 years, 36/42= 85.7%; ≥ 18 years, 41/48= 85.4%, p=n.s.), with a statistically significant difference between the second and third cycle (75.8% vs 89%, p=0.018). RFS at 15 months 81%; long-term responses, lasting for a median time of 8 months (4-24), were 67/90 (74.4%).

In both studies, therapy was well tolerated. A schedule of three cycles of HD-DXM pulses will be compared with standard prednisone therapy (e.g.1mg/Kg/day) in a next randomized GIMEMA trial.
INTRODUCTION

Idiopathic Thrombocytopenic Purpura (ITP), an autoimmune disease, is characterized by early platelet destruction induced by autoantibodies directed against specific glycoproteins of platelet surface.\textsuperscript{1,2} Even if up to now corticosteroids have been widely recognized as the most appropriate first-line treatment, the best therapeutic approach to this disorder is still a matter of debate. Indeed, prednisone or prednisolone is administered, as front-line therapy, to most ITP adult patients who need to be treated. The starting dose is usually 1mg/Kg/day and usually continued for 2-4 weeks. If a raised platelet count is attained, the dose is gradually tapered over several weeks. With this approach usually an initial response rate of about 50-60% is obtained, while long-term remission rate, after therapy discontinuation, ranges between 10 and 20\%\textsuperscript{3-7} or more (25\% long-term complete remissions, as reported by Portielje et al\textsuperscript{8}).

Furthermore, either prednisone/prednisolone, at standard/high doses or high-dose intravenous immunoglobulin (HD-IVIg) are also considered as first-line treatments in children affected by ITP needing therapy. With these approaches a long-term response rate of about 80\% is reached\textsuperscript{9-11}. Nevertheless, a controversy persists whether to give drug therapy to ITP children with mild or moderate bleeding symptoms, despite of very low platelet count, as a rapid spontaneous remission, without any therapy, is possible. The published practice guidelines for the treatment of ITP of American Society of Hematology (ASH)\textsuperscript{6} and of British Society of Hematology (BSH)\textsuperscript{12}, both based on expert opinions, give different recommendations. The former guidelines favour treatment based on low platelet count, while the latter ones prefer a “wait and watch” approach. However, the most part of randomized clinical trials concerning the treatment of ITP children, have considered the rise of platelet
count as the unique relevant outcome. In fact, at present, there is a lack of randomized trials focusing also on bleeding, quality of life, adverse effects and costs as well.\textsuperscript{13,14}

The administration of pulsed high-dose dexamethasone (HD-DXM) at a dose of 40mg/day given orally according to a four-day course, repeated each 28 days, for six consecutive times in adult ITP refractory to several therapy lines, dates back to the mid nineties. Indeed, in a small cohort of patients a response rate of 100\% has been observed\textsuperscript{15}, but in other studies, the same approach was not so successful\textsuperscript{16-19}. Andersen’s purpose\textsuperscript{15} was mainly based on some considerations: 1) efficacy of pulsed corticosteroids in reducing immunoglobulin production in clonal B-cell disorders, 2) long half-life and good tolerability of DXM when given in high doses, 3) very low cost of corticosteroids. Moreover, the efficacy associated with acceptable tolerability of pulsed HD-DXM was previously reported in the treatment of multiple myeloma\textsuperscript{20}. In a very recent study, HD-DXM was given in a single four-day course (40mg/day, orally) in previously untreated adult ITP patients with very encouraging results: initial response rate was 85\%, relapse rate 50\% and sustained response 42\%. Moreover, all relapsed patients had a response to a second therapy course, but only a minority of them (18.5\%) showed a persistent response after discontinuation of maintenance therapy\textsuperscript{21}. Although it seems that HD-DXM has a better response rate than conventional prednisone doses, we do not know whether results could be improved by reducing relapse rate, and, thus, improving persistent responses, as there are no randomized studies.

In this paper we show the results of two different prospective pilot studies, a monocentre study and a multicentre study, concerning the use of pulsed HD-DXM in newly diagnosed, untreated ITP patients.

The aim of the first mentioned study was to evaluate the feasibility, compliance and efficacy of the Andersen’s protocol, proposed for refractory ITP, in untreated newly diagnosed adult
patients. The study was conducted from February 1996 to June 2000. The results were very promising in what concerns efficacy. Nevertheless, we observed an early discontinuation of therapy in more than 48% of patients, either due to medical decision or to low compliance to a long-lasting treatment. On the basis of this preliminary experience, the GIMEMA ITP Working Party planned a multicentre pilot study in which pulsed HD-DXM was given as first-line treatment according to a modified therapy schedule, by reducing courses number (from 6 to 4) and by shortening time intervals between them (14 days instead of 28). Adults and children with ITP were enrolled in this second study. The objectives were to evaluate efficacy, safety and patients’ compliance.

METHODS

Inclusion criteria

Monocentre pilot study

Eligible subjects for this study were previously untreated adult patients (age ≥20 to ≤65) with newly diagnosed ITP and a platelet count of ≤ 20 x 10⁹/L or > 20 x 10⁹/L if bleeding symptoms were present, according to the below reported score (table 1). Enrollement took place between February 1996 and June 2000 at the Haematology Department of the University “La Sapienza” of Rome, Hospital “Policlinico Umberto I”, Italy.

GIMEMA multicentre pilot study

Eligible population in this study was previously untreated patients (age ≥ 2 to ≤ 70) with newly diagnosed ITP and a platelet count of ≤ 30x10⁹/L or > 30x10⁹/L if bleeding symptoms were present, according to the below reported score (table 1) Patients were enrolled from June 2001 in 16 “GIMEMA” Centres. We chosen a 18-years cut point for segregation between “adults” and “children”, because in Italy this is the age limit for referring a patient to
an adult centre and not to a pediatric ward. Moreover, among the < 18 year population, we considered also a segregation at age of 10 years between pre/ peripubertal and post-pubertal age.

Both our pilot studies, did not provide a control group.

In both studies, each enrolled patient or his/her legal guardian signed an informed consent form. This research was approved by the council of Biotechnology and Hematology department of the University of Rome “La Sapienza.”

Exclusion criteria

In both studies the exclusion criteria were as follows: pregnancy, hypertension, cardiovascular diseases, diabetes, liver and kidney function impairment (e.g.: ALT, AST > 2 times upper normal limit; creatinine > 1.8 mg/dL respectively), HCV, HIV, HBsAg seropositive status and a recent viral illness or intake of non corticosteroids anti-inflammatory drugs, both occurred within one month before diagnosis. Moreover, the presence of autoimmune haemolytic anaemia and connective tissue diseases was also considered as an exclusion criterion. In both studies, patients in whom bone marrow aspirate was not performed were excluded.

Diagnosis of ITP

Diagnosis of ITP was based on to commonly adopted criteria: patient’s medical history, physical examination, complete blood cells count and cytomorphological examination of peripheral blood smear\textsuperscript{6,12}, in which no alterations of erythrocytic and leukocytic series should be present. To confirm the diagnosis, bone marrow aspirate was performed to all patients and only those with presence of a normal or increased number of megakaryocytes,
without pathological alterations of erythroblastic, granuloblastic and lymphocytic series, were included in the study.

Determination of autoimmunity markers (antinucleus, antimitochondria, anticardiolipin antibodies) and direct antiglobulin test (DAT) was also performed in all enrolled patients. Bleeding symptoms were classified according to a “score system” graded from 0 to 4, as reported in table 1. Bleeding symptoms were considered present if bleeding score was graded 1 or more.

Therapy schedules

In the monocentre study the therapy schedule was as follows: DXM was administered intravenously, at 40 mg single daily dose, for 4 consecutive days, every 28 days. A total of 6 cycles was planned. If platelet count remained $\leq 20 \times 10^9/L$ between courses or bleeding symptoms related to thrombocytopenia were present, therapy with prednisone at 0.25 mg/Kg/body weight/day, p.o. was given. Complete blood cell count was performed on days 5 and 28 of each cycle. Response evaluation was assessed after completion of therapy on day 28 of the latest performed cycle.

In the GIMEMA multicentre pilot study, oral or intravenous DXM was given as single daily dose of 40 mg for 4 consecutive days, every 14 days, for 4 courses. In patients younger than 15 years old the daily dose was 20 mg/m$^2$ (maximum 40 mg/day). Complete blood cell count was performed at the following days: 0-4; 14-18; 28-32; 42-46; 60. If platelet count was $\leq 30 \times 10^9/L$ or bleeding symptoms related to thrombocytopenia were present, low-dose DXM (0.035 mg/Kg/body weight/day, p.o.) between courses was given. Response evaluation was made at day 60 after treatment start.
In both studies a therapy course was defined as the time interval between the first DXM pulse and the fourth one. A therapy cycle was defined as the time interval between the start of a given therapy course and the start of the following course, including the gap between them.

Response evaluation

In both studies the response was evaluated according to the following criteria: Complete Response (CR) defined as platelet count $\geq 150 \times 10^9$/L; Partial Response (PR) defined as platelet count $\geq 50 < 150 \times 10^9$/L; Minimal Response (MR) defined as platelet count $> 20 < 50 \times 10^9$/L in the monocentre study and $> 30 < 50 \times 10^9$/L in the multicentre study; no response (NR) defined as platelet count $\leq 20 \times 10^9$/L in the monocentre study or $\leq 30 \times 10^9$/L in the multicentre study, or persistence of bleeding symptoms related to thrombocytopenia. CR, PR or MR were stated in absence of any other treatment for ITP. Persistent Complete, Partial or Minimal Response (pCR, pPR, pMR), were defined as the response lasting at least two months after treatment discontinuation.

Adverse events were graded following the CTC-NCI version 2.0.\textsuperscript{22}

Follow-up (FU) was defined as the time elapsing between diagnosis and the last available assessment.

Relapse was defined as a platelet count decrease $\leq 20 \times 10^9$/L (monocentre study) or $\leq 30 \times 10^9$/L (multicentre study) or presence of bleeding symptoms due to thrombocytopenia after the achievement of initial response.

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

Statistical Analysis
Differences in the distributions of variables between groups of patients were analyzed by $\chi^2$ or Fisher’s exact test.

Relapse-free survival was measured from the date of response achievement to the date of relapse, censoring patients alive without relapse.

The probability of RFS was calculated using the Kaplan-Meier method and the prognostic value of potential factors was assessed using the log-rank test with stratification for risk group.

The multivariate analysis of RFS was done using the Cox proportional hazard model.

All analyses were two tailed and were considered statistically significant when $p \leq 0.05$.

All analyses were performed using SAS v.8.02.

RESULTS

Monocentre study

Thirty-seven eligible previously untreated ITP patients were enrolled in this study. The main clinical characteristics of these patients are listed in table 2.

All patients underwent a mean of 5 therapy cycles (min-max 3-6); 19/37 patients (51.4%) completed 6 cycles. Treatment was stopped before completion in 18 patients (48.6%) due to poor compliance in 9 patients (5 CR, 3 PR, 1 MR), medical decision in 4 (2 CR, 2 NR) and adverse events in 5 (4 CR, 1 NR).

No patient showed positivity of autoimmune markers and or DAT.

Responses were reached in 33/37 patients (89.2%): CR in 23 (62.2%), PR in 8 (21.6%); MR in 2 (5.4 %) and 4 were non responder patients (10.8 %). In the responder patients
(CR+PR+MR) median platelet count was 204 x 10^9/L (min - max 25 - 373); in non responders median was 12 x 10^9/L (min - max 5 – 20).

No statistically significant difference of overall response rate was shown by sex (males 16/18, 88.9%; females 17/19, 89.4%; p =n.s.).

No statistically significant difference was found between the overall response rate (CR+PR+MR), reached by patients who completed all six therapy cycles (18/19, 94.7%) and the one obtained by patients who completed 3, 4 or 5 cycles, considered altogether (15/18, 83.3%), (p= n.s.). In what the comparison of quality of response concerns (CR vs PR+MR), no statistically significant difference was found between the two above mentioned groups: CR 12 vs 11; PR+MR 6 vs 4 (p= n.s.).

Median FU of 37 evaluable patients was 25 months (min-max 6-77).

Among the 33 responder patients, 8 (24.2%) relapsed after a median time of 19.5 months (min-max 4-49) after response achievement. At relapse, median platelet count was 15x10^9/L (range 8-19 x 10^9/L).

Relapse-free survival of all evaluable responder patients (n = 33) was estimated 90% (C.I. 95%: 78.3-100) at 15 months and 58% (C.I. 95%: 32.9-83.3) at 50 months (figure 1A).

Relapse–free survival according to the number of cycles (3, 4, 5 vs 6) at which the response was obtained did not show any statistically significant difference: after 6 cycles 94% at 15 months (C.I. 95%: 82.9-100), after 3-5 cycles 84% (C.I. 95%: 62.5-100; p=n.s.) (figure 1B).

Long-term responses, lasting for a median time of 26 months (min-max 6-77) without relapses and without any therapy, were observed in 25/33 responder patients (75.8%) that is 25/37 (67.6%) of all evaluable patients; in particular, pCR were 20/25 (80%), pPR 4/25 (16%), pMR 1/25 (4%). Median platelet count at last control was 220x10^9/L (min-max 40-281x10^9/L).
Five adverse events were observed in 5/37 patients (13.5%): hypertension (CTC-NCI grade 3), anxiety (CTC-NCI grade 2), gastric distress (CTC-NCI grade 2), cataract (CTC-NCI grade 2), bronchial pneumonia (CTC-NCI grade 2). In these cases treatment with HD-DXM had to be stopped at different time points (after the end of the 4th, 3rd, 5th, 4th and 5th cycle, respectively).

During therapy cycles, no bleeding complications and no salvage or emergency therapies, like platelet transfusions or HD-IVIg, were required.

**GIMEMA multicentre pilot study**

Ninety-five eligible previously untreated ITP patients were enrolled in this study. The main clinical characteristics of these patients are listed in table 3. Ninety patients (males 32, females 58) who completed all 4 therapy cycles were evaluable for response at day 60: four patients were lost to FU (2 aged less than 18 years) after the second therapy cycle and one adult patient stopped treatment early due to gastric distress (CTC-NCI grade 3) after the third course.

No patient showed positivity of autoimmune markers and or DAT.

Responses were reached in 77/90 patients (85.6%): CR in 58 (64.5%), PR in 18 (20%), MR in 1 (1.1%); non responder patients were 13 (14.4%). In the responder patients (CR+PR+MR) median platelet count was 214 x 10^9/L (min – max 35 – 676); in non responders median was 14 x 10^9/L (min – max 9 – 25).

No statistically significant difference of overall response rate was shown by sex (males 29/32, 90.6%; females 48/58, 82.8%; p=n.s.). The overall response rate was similar in patients classified by age (< 18 years, 36/42= 85.7%; ≥ 18 years, 41/48= 85.4%, p=n.s.).

Response evaluation by therapy cycle showed that overall response rates (CR+PR+MR) after the first, the second, the third and the fourth cycle were as follows: 69.5% (66/95), 75.8%
(72/95), 89% (81/91), 85.6% (77/90), respectively. No statistically significant difference of overall response rates was found between the first and the second cycle (p= n.s.), while a statistically significant increase was found between the first and the third cycle (p=0.001) and the second and the third one (p=0.018). After the fourth cycle, no further rise was recorded (p=n.s.). Even if the overall response rate in patients under and over 18 years was similar (85.7% vs 85.4%), a progressive improvement of the quality of response (CR) from the first therapy cycle to the fourth one was observed, in particular in patients <18 years (figure 2). Moreover, the quality of response (CR rate vs PR+MR rate) achieved by the two above mentioned groups was better in terms of statistically significance in patients aged <18 years (p= 0.039) (fig 2). Considering the segregation at 10 years cut point of evaluable patients aged <18 years (32/42 aged <10 years and 10/42 aged ≥ 10 years), we noted that total response rate (CR+PR+MR) was 87.5% (28/32) and 80% (8/10), respectively.

In all evaluable 90 patients, considered as a whole and separated in age classes, we have evaluated the early rise of platelet count at the 4th day of 1st therapy cycle, that is the day after the end of the 1st therapy course (control at day 4 as the GIMEMA study provided). Moreover, we evaluated, on the same day, how many subjects (adults and children) obtained a rise of platelet levels >30x10^9/L (MR), ≥50x10^9/L (PR) or >20x10^9/L (in patients with platelet count ≤ 20x10^9/L at enrollement). The results are shown in table 4: adults and children behaved similarly in what concerns the median value of platelet count (p=n.s) and the rate of patients that have reached the above mentioned values (p=n.s). In particular, 89% of evaluable children reached platelet levels >20x10^9/L, 81% > 30 and 67% ≥ 50x10^9/L. If we also considered the two children subgroups, <10 and ≥ 10 years, they behaved similarly.

Median FU of 90 evaluable patients was 10 months (range 3-24).
After a median time of 6.5 months (min-max 3-10) from response achievement, 10/77 (13%) responder patients relapsed. Median platelet count at relapse was 21x10^9/L (min-max 3-29x10^9/L). The relapse rate was lower in patients younger than 18 years old (1/36: 2.7%), when compared to that of patients over 18 years (9/41: 22%) (p=0.01).

Overall RFS was 81% (C.I: 95%: 70.6-92.3 at 15 months). No difference regarding RFS was shown according to sex in responder patients (p=n.s). Relapse-free survival according to age was 96% (C.I. 95%: 88.8-100.0 at 15 months) for patients < 18 years and 60% (C.I. 95%: 37.3-83.5 at 15 months) for patients ≥ 18 years: this difference was statistically significant (p=0.0009) (figure 3A). Relapse-free survival according to the quality of initial response was 87% (C.I. 95%: 76.1-98.1 at 15 months) for patients who achieved a CR and 65% (C.I. 95%: 39.4-91.0 at 15 months) for patients who reached PR or MR, p=0.05 (figure 3B).

Nevertheless, due to the association between the two factors (age and quality of initial response) (p=0.003) only age stays significant in a multivariate Cox model (table 5). In other words, in the same age class the quality of initial response does not influence the outcome.

Long-term responses, lasting for a median time of 8 months (min-max 4-24) without relapses and without any therapy, were observed in 67/77 responder patients (87%), that is, 67/90 (74.4%) of all evaluable patients; in particular: pCR 53/67 (79.1%), pPR 11/67 (16.4%), pMR 3/67 (4.5%). The overall persistent response rate in patients < 18 years (35/36) was 97.2% and in those ≥ 18 years (32/41) was 78% (p=0.015).

Treatment with pulsed HD-DXM was well tolerated. Adverse events were recorded in 2/95 enrolled patients (2.1%), both adults: transitory hypertension in one patient, gastric distress in another patient who was withdrawn from treatment after the third therapy course.

Both events were of grade 3 (CTC-NCI 2.0). No patient aged <18 years discontinued the treatment for adverse events related to therapy.
During therapy cycles, no bleeding complications were recorded and no salvage or emergency therapies, like platelet transfusions or HD-IVIg, were required. Non responder patients (29 after 1st cycle, 23 after 2nd cycle, 10 after 3rd cycle) received low-dose DXM between courses.

DISCUSSION
The rationale of the initial therapeutic approach of ITP is either to overcome bleeding risk or to achieve a stable response, possibly without any further treatment, and thus, avoiding long-term side effects as infections or metabolic alterations.

It is well known that, up to now, prednisone or prednisolone, is considered the most largely used therapeutic approach as first-line treatment for ITP patients, especially when adults, even if consistent data regarding the best dosage are missing. With prednisone or prednisolone given at standard daily dose around 1 mg/Kg for 2-4 weeks, an initial response rate of 50-60% is generally obtained, but long-term response rate, without any therapy, is very low (10-25%) 3,5-7.

Moving from the Andersen’s experience 15, concerning the use of pulsed HD-DXM given in resistant/refractory ITP with very satisfactory results, we planned a first pilot monocentre study with the aim of evaluating efficacy, safety and tolerability of this treatment as first-line therapy in previously untreated adult ITP patients, according to a six cycles therapy schedule. Initial response rate was very encouraging (about 90%) and long-term response was about 68% (25/37, with 20 CR) in all evaluable patients (median FU 26 months). Notwithstanding the number of therapy cycles administered (6 or less), there was no statistically significant difference on the initial response rate and on RFS at 15 months. Nevertheless, a shorter therapy schedule could be advisable, especially, if we consider that 9 patients discontinued treatment before completion of therapy due to poor compliance. On the basis of these
encouraging results, the GIMEMA ITP Working Party planned a multicentre pilot study with the aim of obtaining a better compliance and feasibility, together with a satisfactory efficacy, modifying the first study therapy schedule by reducing the number of therapy courses (four instead of six) and the interval between them (14 days instead of 28).

The GIMEMA multicentre pilot study showed that the pulses of HD-DXM, given at shorter time intervals, were feasible and well tolerated by adults and children with ITP. Patients’ compliance was good. Efficacy was proved by high initial response rate (about 86%) and a low overall relapse rate (13%), with a RFS of 81% at 15 months. The greatest overall initial response rate was reached after completion of the third therapy cycle, without any further significant increase after the fourth cycle, even if the quality of response (CR versus PR+ MR rate) tends to improve through cycles, until the fourth one (figure 2).

In the GIMEMA multicentre pilot study it was planned to enrol adults and children with ITP; despite initial overall response rate was similar in patients under and over 18 years old (85.7% vs 85.4%), however, children outcome during the FU was better than that of adults. In fact, the patients under 18 years old showed a lower relapse rate than older patients (2.7% vs 22% p= 0.01) and a higher sustained response rate in time. (figure 3A). Even if initial response rate and long-term outcome of children is similar to that reported in previous published series, however, due to the rapid achievement of safe platelet count just at the end of the first therapy course in a large part of patients, we did not experience any adverse events related to bleeding during the early period of treatment. It is noteworthy that this is true for children belonging to both age subgroups, under and over 10 years, although there was a discrepancy as it concerned the number of evaluable patients (32 vs 10). (table 4). The prevention of severe bleedings, indeed, is one of the major aims of children ITP treatment. The quality of initial response rate influence the long-term response. In fact, patients who obtained a CR showed a better outcome, with a higher RFS rate, than patients who reached
PR or MR (87% vs 65%) (figure 3B). In any case, on the multivariate analysis the only independent factor influencing the outcome is age (table 5).

As for adult patients, comparing the results obtained in both studies to those reported in the literature with conventional treatment, a better initial response rate and an increased long-term response rate (about 67% versus 10-25%) was observed.

In the multicentre study we observed a better patients’ compliance, probably due to a shorter duration of the therapy schedule, without relevant side-effects. Moreover, nor bleeding complication, nor emergency therapies were recorded during therapy cycles in adults or in children. In fact, according to the GIMEMA protocol, non responder patients received low-dose DXM between therapy courses.

The results obtained by the GIMEMA multicentre pilot study in adults are comparable to those recently reported by Cheng et al. for the initial response rate (85% vs 85%). However, the relapse rate of 22% observed in the GIMEMA study, is very different from that observed by Cheng et al. who reported a 50% of relapse rate within 6 months from response achievement. As a consequence, we have obtained 66.7% (32/48 evaluable adult patients) of persistent responses, without any therapy, while, in the Cheng et al study it was reported a persistent response rate of 42% \textsuperscript{21}. Furthermore our data seem to be similar to those of Borst et al. \textsuperscript{23}, who more recently reported a long-term response of 59%. However, they observed 22% of adverse events, which in our two studies were 13.5% and 2.1%, respectively.

Therefore, our results confirm that HD-DXM can be proposed as first-line treatment of both adults and children with ITP. Moreover, repeated cycles of therapy seem to be more efficient than only one cycle as proposed by Cheng et al. to achieve long-term response, especially in adults. In fact, in the GIMEMA experience a persistent response after 4 therapy cycles is achieved on about 67% of adults patients, as compared to 42% of response obtained by Cheng et al. with only one cycle.
Furthermore, because no statistically significant difference as it concerns the initial overall response rate between the third and the fourth cycle was noted, only three therapy cycles, could be more appropriate, reaching a better patients’ safety and tolerability, keeping the efficacy. In conclusion, randomized clinical trials are necessary to confirm these issues, and thus, pulses of HD-DXM given according to three cycles will be proposed in a next randomized “GIMEMA” clinical trial, versus conventional prednisone treatment, given at daily dose of 1mg/Kg for 4 weeks, for previously untreated adult ITP patients.

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dexamethasone as a first- and second-line treatment of idiopathic thrombocytopenic
Patients at risk 33      Events: 8
Probability of relapse free survival
97% (C.I. 95%: 90.8 - 100) at 6 months
90% (C.I. 95%: 78.3 - 100) at 15 months
58% (C.I. 95%: 32.9-83.3) at 50 months

patients at risk 18      events 4

Probability of relapse free survival
cycles 6: 94% (C.I.95%:82.9%-100%) at 15 months
cycles 3-4-5: 84% (C.I. 95%: 62.5%- 100%) at 15 months

Figure 1: Monocentre pilot study -
A: Relapse Free Survival
B: Relapse Free Survival according to cycle
Figure 2: GIMEMA Multicentre pilot study. Chart: CR evaluation according to therapy cycles and age. Table: Quality of initial response by age
A

< 18 years: 96% (C.I. 95%: 88,8 -100) at 15 months

≥ 18 years: 60% (C.I. 95%: 37,3 – 83,5) at 15 months

p=0.0009

B

CR: 87% (C.I. 95%: 76,1 - 98,1) at 15 months

PR+MR: 65% (C.I. 95%: 39,4 - 91,0) at 15 months

p =0.050

Figure 3: GIMEMA multicentre pilot study.
A: Relapse Free Survival by age
B: Relapse Free Survival according to quality of initial response
Major mucous and/or parenchymal haemorrhage with copious loss of blood and with sequelae and/or life-threatening or death

Major mucous haemorrhage with copious loss of blood without sequelae

Ecchymoses and/or dripping with moderate loss of blood

Petechiae

<table>
<thead>
<tr>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>Petechiae</td>
<td>Ecchymoses and/or dripping with moderate loss of blood</td>
<td>Major mucous haemorrhage with copious loss of blood without sequelae</td>
<td>Major mucous and/or parenchymal haemorrhage with copious loss of blood and with sequelae and/or life-threatening or death</td>
</tr>
</tbody>
</table>

Table 1: Grade and type of bleeding symptoms
<table>
<thead>
<tr>
<th>Patients</th>
<th>37</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>18/19</td>
</tr>
<tr>
<td>Median Age (years)</td>
<td>34</td>
</tr>
<tr>
<td>min-max</td>
<td>20-58</td>
</tr>
<tr>
<td>Median platelet count (x10⁹/L)</td>
<td>7</td>
</tr>
<tr>
<td>min-max</td>
<td>1-22 *</td>
</tr>
<tr>
<td>Bleeding score:</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2: Monocentre pilot study: characteristics of enrolled patients
*two patients with platelet count 22x10⁹/L had bleeding score 1*
<table>
<thead>
<tr>
<th>PATIENTS</th>
<th>TOTAL</th>
<th>AGE ≥2&lt;18 YRS</th>
<th>AGE ≥18 ≤70 YRS</th>
</tr>
</thead>
<tbody>
<tr>
<td>M/F</td>
<td>34/61</td>
<td>21/23</td>
<td>13/38</td>
</tr>
<tr>
<td>Median Age (years) &lt;br&gt; min-max</td>
<td>20 &lt;br&gt; 2-70</td>
<td>5.7 &lt;br&gt; 2-17.9</td>
<td>35.1 &lt;br&gt; 19.9-70</td>
</tr>
<tr>
<td>Median platelet count (x10^9/L) &lt;br&gt; min-max</td>
<td>9 &lt;br&gt; 1-35*</td>
<td>8 &lt;br&gt; 1-26</td>
<td>10 &lt;br&gt; 1-35*</td>
</tr>
<tr>
<td>Bleeding score: &lt;br&gt; (available in 68/95 patients)</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 3: GIMEMA Multicentre pilot study: characteristics of enrolled patients

°° >2<10 yrs: 34 (M/F: 16/18); >10<18yrs: 10 (M/F: 5/5)
* two adult patients (age 30 and 39 years) with platelet count 32 and 35x10^9/L, had bleeding score 2 and 3, respectively.
Table 4: GIMEMA Multicentre pilot study: platelet count of evaluable after the end of 1st therapy course

* patients with platelet count ≤ 20x10⁹/L at enrollement
<table>
<thead>
<tr>
<th>Type of response (CR vs PR+MR)</th>
<th>p-value</th>
<th>hazard ratio</th>
<th>lower CL95%</th>
<th>upper CL95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age &lt; 18 yrs vs ≥ 18 yrs</td>
<td>0.0182</td>
<td>12.592</td>
<td>1.537</td>
<td>103.159</td>
</tr>
</tbody>
</table>

Table 5: GIMEMA Multicentre Pilot Study – Multivariate analysis for Relapse Free Survival
Therapy with high-dose dexamethasone (HD-DXM) in previously untreated patients affected by idiopathic thrombocytopenic purpura. A GIMEMA experience

Maria Gabriella Mazzucconi, Paola Fazi, Sayla Bernasconi, Giulio De Rossi, Giuseppe Leone, Luigi Gugliotta, Nicola Vianelli, Giuseppe Avvisati, Francesco Rodeghiero, Angela Amendola, Carlo Baronci, Cecilia Carbone, Stefano Quattrin, Giuseppe Fioritoni, Giulio D’Alfonso and Franco Mandelli

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