



High versus standard dose methylprednisolone in the acute phase of idiopathic thrombotic thrombocytopenic purpura: a randomized study

Carlo L. Balduini, Luigi Gugliotta, Mario Luppi, Luca Laurenti, Catherine Klersy, Carla Pieresca, Gerlando Quintini, Francesco Iuliano, Rossana Re, Pierangelo Spedini, et al.

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Abstract: Therapeutic plasma exchange (PE) is the accepted therapy for thrombotic thrombocytopenic purpura (TTP). Because not all patients obtain remission, other treatment modalities have been used in addition to PE, but no randomized clinical trial evaluated their efficacy. The aim of this multicentric study was to compare the effectiveness of standard- versus high-dose methylprednisolone as an adjunctive treatment to PE in the acute phase of TTP. Sixty patients with idiopathic TTP were randomized to receive standard-dose (1 mg/kg/die i.v.) or high-dose methylprednisolone (10 mg/kg/die for three days, thereafter 2.5 mg/kg/die) in addition to PE.

Both dosages of steroids were well tolerated. At the end of induction therapy (day 23), the percentage of patients failing to obtain complete remission was significantly higher in the standard-dose (16/30) than in the high-dose group (7/30). Also the number of cases without a good response at day 9 and the number of deaths were higher in the standard-dose arm, but the differences did not reach the statistical significance. Results of present study indicate that the association of PE with high-dose instead of standard-dose steroids reduces the percentage of TTP patients that fail to achieve complete remission.

Response to Reviewers: Reviewer #1: The authors have proved that the association of plasma exchanged with high-dose methylprednisolone instead of standard-dose reduces the percentage of TTP patients that failed to achieve complete remission. This observation has important clinical implication.

I have no major remarks

Minor remarks: Activity of ADAMTS 13 and autoantibodies against ADAMTS 13 were not tested. In my opinion this paper can be published in Annals Of Hematology in the present form.

Reviewer #2: General:

In this randomized clinical trial Balduini and colleagues compared low-dose vs. high dose steroids as an adjunctive treatment to plasma exchange with fresh frozen plasma / cryosupernatant in 60 patients suffering from acute TTP. In the low-dose arm more patients (13/30 vs. 7/30, $p=0.17$) failed to achieve a good response at day 9 (primary endpoint of the study) and also more patients failed to achieve complete remission (16/30 vs. 7/30; $p=0.03$). Also the number of death (4 vs. 1) was higher, this was however not statistically significant. The authors conclude that plasma exchange in combination with high dose steroids is superior to low-dose steroids.

Over the years the Italian TTP study group has been able to conduct several randomized clinical trials in the setting of acute TTP addressing open questions in the field where many other groups have failed to do likewise due to lack of suitable patient numbers and the group's work demonstrates what is possible through collaboration in the field of rare disorders. Although I admire the efforts of the group very much, I can't understand why even today they are not able to present ADAMTS13 parameters for their patients. This was ok 12 years ago when they presented their study on anti-platelet drugs as an adjunctive to PE (Bobbio Pallavicini et al. Haematologica 1997) and ADAMTS13 assays were not widely available. Nowadays however this severely reduces the impact of their work particularly so when the topic is immunosuppression. There are at least 4 different laboratories in Italy doing ADAMTS13 assays and in case of a conflict of interest within in Italy there are number of other labs in Europe who would probably willing to help out.

Problems:

1.) Patients:

- The authors should indicate the time frame of accrual of patients for this study.

We now state in the section "Patients, materials and methods" that patients have been enrolled from 2000 to 2006.

- How did the authors determine the number of patients per arm needed?

Concerning sample size, we calculated that 30 patients per group would be able to elicit a risk difference of 37% (95%CI 13-60%) when the rate of failure to achieve good response at day 9 in the standard dose group is 60%, with a 80% power and a two sided significance level of 5%.

This information is now given in the section "Patients, materials and methods": "Study end points and statistical analysis".

- Randomization: I think that the differences in the male to female ratio in the different treatment arms may be a problem. The classical TTP case with severe autoantibody mediated ADAMTS13 deficiency is typically a female between 25-40 years or so. It seems likely that particularly patients with severe autoantibody mediated ADAMTS13 deficiency benefit from a high-dose steroid regimen - this was also the rationale for the study - and the over-representation of females in the high dose group could have an impact on the results. This should be discussed.

We thank the reviewer for this interesting observation. Taking into account his suggestion, we calculated the results at day 23 for male and female patients separately and concluded that males achieved complete remission more frequently than females both in the high-dose arm and the standard-dose arm. However, due to the small number of enrolled patients, we believe that these data do not allow to reach any conclusion. Moreover, due to our failure to obtain ADAMTS13 data in many cases (see below), we suggest that discussing the correlations between gender, autoimmunity and efficacy of steroid therapy is useless in the context of our paper. However, in the section "Patients, materials and methods": "Patients" of the revised manuscript, we now underline that the male/female

ratio (as well as the percentage of patients with neurological involvement) was different in the two treatment arms.

- Reasons for death should be described.

This information is now given in the section "Results".

- PE treatment usually required large indwelling lines, which harbor a risk for systemic infections, particularly in immunosuppressed patients. According to reports from the Oklahoma TTP/HUS registry a considerable amount of patient experience bacteremia or even sepsis during treatment for acute TTP bouts. The authors should make a comment on whether any of their patients experienced such a problem and/or whether they received prophylactic antibiotics. An infection results in stimulation of the immune system and with it possible to an increased production also of anti-ADAMTS13 antibodies and could have an impact on the results of the study.

We now state in the section "Results" that, although patients did not receive prophylactic antibiotics during PE, no infectious episode has been reported.

- I have some difficulties to understand how the group decided on the lower steroid dose, as they had used 2mg / kg body weight in their former TTP study, and many other clinicians treating TTP patients use a dose of 1-2mg/kg body weight.

It is true that many clinicians currently use either 1mg/kg or 2mg/kg steroids for TTP patients, and it is also true that in the past we used 2 mg of methylprednisolone/kg. However, in the present study we decided to use 1 mg/kg as standard dose to maximize the difference between high and standard dose, and to have more chances of observing differences between the results obtained by the two treatments.

- I suggest to check all freezers again to see whether the individual researches have stored at least some patients' samples for ADAMTS13 activity testing.

We perfectly agree with the reviewer that the results of ADAMTS13 testing could add further value to our research. The study protocol included testing for ADAMTS13 activity and autoantibodies, but we failed to obtain a number of samples sufficient for statistical analysis. We made every effort to obtain this result and asked the participants in the study to "check their freezers" (and this is one of the reasons why preparation of the manuscript took a very long time), but this attempt was unsuccessful.

2.) Results/Discussion:

- I think that the number of patients refractory (not achieving complete remission) on day 23 is higher than expected from other studies and according to my own experience. This should be discussed and reasons other than inferiority of low-dose steroids as adjunctive treatment should be considered.

Evaluating the results of different treatments in the reported case series of patients with TTP is very difficult, in that differences in the enrolling criteria and in the definitions of responses, as well as in the timing of response evaluation, often preclude a direct comparison. Thus, in the original version of our manuscript we compared the results of present study only with those of a few, similar trials.

We perfectly agree with the reviewer that higher percentages of complete response have been reported in patients treated with PE and 1mg/kg prednisone. For instance, Mintz and coll (Transfusion 2006;46:1693) reported that 89% of 18 patients obtained a CR within 30 days, although some of them relapsed a few days after obtaining remission. On this basis, their data are not directly comparable with our ones at day 23 because of different timing and methods for evaluating responses.

We also know that same trials obtained a percentage of CR lower than our study. For instance, Cataland and coll (Br J Haematol 2006;132:146) described that only 4 of 12 patients receiving PE and 1mg/kg prednisone were in CR at day 30.

In summary, we are convinced that trying to compare the results of trials that are not directly comparable does not allow to reach any firm conclusion, and that only randomized studies offer reliable results.

Based on these considerations and taking into account the reviewer's suggestion, we introduced the following sentence in the section "Discussion":

"A few other studies examine the results obtained in little case series by the association of PEs with 1 mg/kg/die prednisone and describe percentages of complete remission much higher (Transfusion 2006;46:1693) or lower (Br J Haematol 2006;132:146) than those obtained by us. However, differences in the enrolling criteria and in the definitions of response, as well as in the timing of response evaluation, preclude a direct comparison. Anyway, we can not exclude that a remission rate lower than expected in our standard-dose arm overestimated the benefit deriving from high-dose prednisone".

- Table 2 could be left away as the p-values as well as comparison of death rates in the two groups can easily be included in the text.

We suggest that Table 2 offers the possibility to understand the results of our study at a glance. Eliminating this table implies that we have to insert into the text not only the numbers and the percentages of deaths, but also the differences (with the 95% CI and the p values) between standard- and high-dose treatments. This could create confusion. Anyway, in the case the reviewer and the editor will ask us to remove this table, we will do it very quickly.

- To my knowledge the group's anti-platelet study had two arms, one was placebo, the other aspirin and dipyridamole during the acute phase. In both arms patients received also steroids. It seems to me that it would be more appropriate to compare the remission rates of the present study with that in the placebo arm than that in the treatment arm (second paragraph, page 7)

Based on the results of our previous study, aspirin treatment has been programmed for both arms of the present trial. So, we believe that comparing the remission rates of the present study (where patients received anti-platelet treatment) with that in the treatment arm of the previous one (where patients received anti-platelet treatment) is correct.

3.) Language and syntax need some attention:

- remission is achieved rather than obtained; .while ranitidine was administered intravenously when oral administration was not possible rather than patients unable to assume oral therapy etc.

- In addition, there are some repetitions (sentence on randomization page 4; 2nd paragraph on page 6).

We modified the manuscript according to the reviewer's suggestions.

-HIGH VERSUS STANDARD DOSE METHYLPREDNISOLONE IN THE ACUTE PHASE OF IDIOPATHIC THROMBOTIC THROMBOCYTOPENIC PURPURA: A RANDOMIZED STUDY

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Key words: TTP, steroids, plasma exchange, thrombocytopenia

Summary

Therapeutic plasma exchange (PE) is the accepted therapy for thrombotic thrombocytopenic purpura (TTP). Because not all patients achieve remission, other treatment modalities have been used in addition to PE, but no randomized clinical trial evaluated their efficacy. The aim of this multicentric study was to compare the effectiveness of standard- versus high-dose methylprednisolone as an adjunctive treatment to PE in the acute phase of TTP. Sixty patients with idiopathic TTP were randomized to receive methylprednisolone 1 mg/kg/die i.v. or 10 mg/kg/die for three days, thereafter 2.5 mg/kg/die, in addition to PE.

Both dosages of steroids were well tolerated. At the end of induction therapy (day 23), the percentage of patients failing to achieve complete remission was significantly higher in the standard-dose (16/30) than in the high-dose group (7/30). Also the number of cases without a good response at day 9 and the number of deaths were higher in the standard-dose arm, but the differences did not reach the statistical significance. Results of present study indicate that the association of PE with high-dose instead of standard-dose steroids reduces the percentage of TTP patients that fail to achieve complete remission.

Introduction

Treatment with plasma delivered by either exchange [1] or infusion [2] dramatically changed prognosis of thrombotic thrombocytopenic purpura (TTP) and transformed this deadly disease into a curable form. Twenty-five years ago, a randomized study by the Canadian Apheresis Study Group compared plasma exchange (PE) with plasma infusion and concluded that the former was significantly better than the latter, with 78% of patients surviving six month after entry into the study [3].

To further improve prognosis of TTP patients, a number of treatments (anti-platelet agents, steroids, cyclosporine, anti-CD20 antibodies, vincristine, cyclophosphamide, intravenous immunoglobulins, etc) have been empirically added to plasma exchange in single patients or small case series, but none of them has been validated by a controlled study.

Demonstration that an acquired deficiency of the plasma metalloprotease ADAMTS13 induced by autoantibodies against this protein affects most patients of idiopathic TTP [4,5] gave a rational basis for immunosuppressive therapy and authoritative authors [5,6] recommended that steroid therapy should be added to PE in the acute phase of this disorder. However, this logical suggestion has not been supported so far by the results of clinical trials.

To fill this gap, we designed a multicentric, randomized study to assess the efficacy of steroids as an adjunctive treatment to PE in the acute phase of idiopathic TTP. Taking into account the common opinion that avoiding immunosuppressant treatment in control patients could be considered no longer ethical, we compared the effectiveness of standard- versus high-dose methylprednisolone.

Patients, materials and methods

Patients

All patients given a diagnosis of idiopathic TTP at 17 Italian medical centres from 2000 to 2006 were considered for entry into this open-label trial. Eligibility criteria were as follows: platelet count less than $100 \times 10^9/L$, microangiopathic haemolytic anaemia as indicated by red-cell fragmentation on peripheral blood smears and high serum LDH with no other identifiable cause for this (in particular: PTr < 1.5, PTTr < 1.5, and fibrinogen > 100 mg/dL to exclude disseminated intravascular coagulation), creatinine lower than 2 mg/dL, and no associated disease that in the

1 opinion of the attending physician rendered the patient unable to tolerate the treatment. Patients
2 with a history of TTP were not excluded from the study whenever the previous episode did not
3 occur in the last three months.
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5 Main characteristics of enrolled patients are reported in Table 1. Although the two treatment arms
6 were well-balanced for what it concerns blood cell counts, LDH levels, age and the presence of
7 fever at onset, both neurological involvement and female sex were more frequent in the high-dose
8 methylprednisolone group. Although, to the best of our knowledge, no study demonstrated that
9 these parameters affect TTP prognosis, we can not exclude that these differences interfered with the
10 results of our trial.
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18 The study was approved by the ethical committee of the IRCCS Policlinico San Matteo Foundation,
19 Pavia, and a written informed consent was obtained from all patients.
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23 *Study design* 24

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27 Apheresis treatment consisted of daily 1.5 plasma volume exchange on the first two days, then
28 single volume exchanges on 5 of the next 7 days. Fresh-frozen plasma was used as replacement
29 fluid in the first procedure, while cryosupernatant (Rock et al, 1996) was used in the following
30 exchanges. Cryosupernatant was used based on a pilot study by the Canadian Apheresis Group
31 suggesting that this replacement fluid was more effective than fresh frozen plasma [7]. However, a
32 subsequent, randomized study by the same group failed to confirm this finding and concluded that
33 the two treatments were equivalent [8].
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42 Patients received aspirin (5 mg/kg/die i.v.) whenever their platelet count was higher than $30 \times 10^9/L$.
43 Misoprostol (200 mcg orally 4 times daily) was used to prevent gastric ulceration, while
44 ranitidine was administered intravenously when oral administration was not possible. Packed red
45 cells were transfused in order to maintain haemoglobin level above 8 gr/dL. Platelet concentrates
46 were not permitted, with the only exception of patients with very low platelet counts and life-
47 threatening haemorrhages.
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54 At admission, patients were centrally randomized (1:1 web-based randomization with the sequence
55 of treatments randomly permuted in blocks of varying size) to standard-dose (1 mg/kg/die i.v.) or
56 high-dose methylprednisolone (10 mg/kg/die i.v. for three days, thereafter 2.5 mg/kg/die i.v.).
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60 Whenever possible, methylprednisolone was administered after PE. In case corticosteroid treatment
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was required before PE, it has been assumed that half of the drug was removed during the procedure and subsequent administration was calculated accordingly to reach the programmed daily dose.

Response to therapy was first evaluated at day 9, after 7 PEs, according to the following criteria: good response, defined as platelet count more than $100 \times 10^9/L$ for two consecutive days without deterioration in the neurological status; poor response, defined as platelet count between 50 and $100 \times 10^9/L$ with an increase in platelet count of more than 100% with respect to baseline without neurological worsening; no response, defined as platelet count less than $50 \times 10^9/L$ or platelet increase less than 100% with respect to baseline and/or neurological worsening.

Patients with good response at day 9 received 5 additional PEs during the next two weeks and continued for one week the standard- or the high-dose methylprednisolone therapy according to randomization, then half a dose for an additional week. Patients with poor response underwent 7 PEs during the next two weeks and continued steroid therapy as patients with good response. Non-responding patients exited the study and were treated at their physicians' discretion.

Patients were finally evaluated at day 23 for complete remission, defined as an increase of platelets to more than $150 \times 10^9/L$, normalization of LDH value and improvement in neurological status.

Study end points and statistical analysis

Primary end-point was failure to achieve “good response” at day 9 after a course of 7 PEs.

Secondary ends points were "less than complete response" or death at day 23.

Data were presented as counts and percent if categorical and as median and 25th-75th percentiles if continuous. The two-sided exact Fisher test was used to test the statistical significance of the differences in the outcomes between the two groups. The 95% confidence intervals (95% CI) for the differences between the two treatment groups were also computed. Analyses were done by intention to treat. Stata 10 (StataCorp, College Station, TX, USA) was used for computation. A p-value<0.05 was considered statistically significant. Statistical analysis was performed by a blinded data analyst. Concerning sample size, we calculated that 30 patients per group would be able to elicit a risk difference of 37% (95% CI 13-60%) when the rate of failure to achieve good response at day 9 in the standard dose group is 60%, with a 80% power and a two sided significance level of 5%.

Results

Thirty patients have been randomized to both standard-dose and high-dose methylprednisolone. All subjects allocated to high-dose treatment received intervention, while one subject allocated to standard-dose died immediately after randomization. Both treatments were well tolerated and no patient had side effects requiring treatment discontinuation. In particular, although our patients did not receive prophylactic antibiotics during PE, no infectious episode has been reported.

At day 9, failure to achieve “good response” occurred in 13 of 30 patients (43.4%) receiving standard steroid dose (4 deaths, 5 “no responses” and 4 “poor responses”) and in 7 of 30 (23.4%) receiving high-dose therapy (1 death, 2 “no responses”, 4 “poor responses”). At day 23, failures to achieve complete remission were 16 (53.4%) in the standard-dose arm and 7 (23.4%) in the high-dose arm. Four patients (13.3%) randomized to standard steroid dose and one patient (3.3%) randomized to high-dose treatment died. The reasons for death were thrombotic (three patients) or haemorrhagic (two patients) intracranial events.

Table 2 shows the statistical significance of the differences observed between the two treatment groups.

Discussion

This randomized, multicentric study has shown that the association of PE with intensive methylprednisolone treatment reduced the risk of treatment failure with respect to standard-dose corticosteroids. The advantage of high-dose over standard-dose at day 9 of treatment was relevant but not significant, while the outcome of intensive treatment was significantly better at the end of the study, at day 23, with 76.6 vs 46.6% of patients achieving complete remission. Also final survival was better in the high-dose group (96.7 versus 86.7%), but the difference did not reach the statistical significance due to the little number of deaths in both arms.

Very few prospective clinical trials have been performed in TTP and comparing their results with those of present study is hampered by differences in the study designs. However, the Canadian Apheresis Group recently performed a randomized, prospective trial to assess whether cryosupernatant is better than fresh frozen plasma as replacement fluid for PE [8]. Patients received 7 PEs during the first 9 days; antiplatelet therapy was optional while steroid were prohibited. Thus, the major difference between the cryosupernatant arm (28 patients) of the Canadian study and present trial is that our patients received corticosteroids. In both studies an assessment of treatment outcomes has been performed at day 9 and a close comparison is therefore possible at this time. It

shows that the percentage of patients with more than 100×10^9 platelets/L was higher in Italian patients treated with high-dose steroids (76.6%) than in Canadian patients (62%). Interestingly, the percentage of Italian patients receiving standard dose methylprednisolone that reached this platelet level was a little lower (56.6%) than Canadian patients. This comparison confirms the efficacy of high-dose steroid, but also suggests that standard-dose methylprednisolone did not improve the effect of PE alone.

Since the Canadian study did not show an advantage to the use of cryosupernatant instead of fresh frozen plasma, we can also compare the results of present investigation with those of a previous trial of the Italian Cooperative Group for TTP [9]. In this study, patients were treated with 2 mg/kg/die methylprednisolone in addition to PEs with fresh frozen plasma and were randomized to receive or not receive anti-platelet agents. At the end of induction therapy, the percentage of complete remissions in the 35 patients randomized to anti-platelet drugs (60%) was lower than in the high-dose steroids arm of present study (76.6%), but higher than in the standard-dose arm (46.6%). Thus, our intensive steroid treatment obtained better results than the 2 mg/kg/die prednisone regimen of the previous one, which, in turn, resulted in a percentage of remission higher than standard-dose steroid therapy of present study.

A few other studies examine the results obtained in little case series by the association of PE with 1 mg/kg/die prednisone and describe percentages of complete remission much higher [10] or lower [11] than those obtained by us. However, differences in the enrolling criteria and in the definitions of response, as well as in the timing of response evaluation, preclude a direct comparison. Anyway, we can not exclude that a remission rate lower than expected in our standard-dose arm overestimated the benefit deriving from high-dose prednisone.

In conclusion, comparison of present study with the few previous comparable trials supports the hypothesis that intensive therapy with methylprednisolone improves PE effectiveness, but does not solve the doubts as to whether lower doses increase the percentage of remission with respect to no steroid treatment.

Effectiveness of high-dose corticosteroids in TTP is supported also by other published studies. In 1991, Bell et al [12] showed that 200 mg of prednisone per day as a sole treatment achieved remission in 48-72 hours in 30 of 54 TTP patients lacking central nervous system abnormalities other than headache. Moreover, Rojnuckarin et al [13] ed rapid and complete responses by pulse,

high dose dexamethasone alone in two patients refractory to PEs. Finally, Toyoshige et al [14] observed a prompt response to 1 g per day of methylprednisolone in one patient who had previously failed to respond to both plasma infusion and PE.

The quick haematological response of TTP to high-dose corticosteroid treatment suggests that its mechanism of action is not the inhibition of antibody production. Unfortunately, we were unable to monitor the levels of ADAMTS13 activity and inhibiting antibodies in our patients, but in the two already cited patients described by Rojnuckarin et al, high dose dexamethasone induced remission without affecting deficiency of ADAMTS13 activity. To explain this phenomenon, it has been suggested that down regulation of various cytokines involved in TTP pathogenesis and/or reduction of endothelial cells activation could be the mode of action of high-dose steroids in this disorder [13,15]. However, no experimental data supported so far this hypothesis. Interestingly, a non-immunological mechanism of action in TTP has been suggested also for cyclosporine, in that it induced remission in some patients independently from improvement in ADAMTS13 activity and suppression of the inhibitor [16].

Disclosure that an acquired defect of ADAMTS13 induced by autoantibodies affects most patients with idiopathic TTP represented a major advance in understanding the pathogenetic mechanisms of this disorder. However, contrasting results have been obtained by the few studies aimed at establishing whether ADAMTS13 testing during the acute episode helps to identify patients' prognosis and can be used to guide their management [17-20]. On this basis, there is general agreement that all patients in the acute phase have to receive the most effective treatment [21], and we suggest that, at least presently, the best option is represented by concomitant PE and high dose corticosteroids. At the opposite, three clinical studies clearly showed that patients with severe ADAMTS13 deficiency during remission have a much higher likelihood of relapse [22-24]. Since reports of single patients or small case series suggested that chimeric anti-CD20 monoclonal antibodies or cyclosporine help to restore normal ADAMTS13 activity and prevent recurrences, it may be that administration of these drugs to patients with a persistent defect of ADAMTS13 improves their long-term prognosis. Obviously, randomized clinical trials are required to confirm this hypothesis.

In conclusion, we suggest that the association of high-dose corticosteroids with PE improves the short-term prognosis of patients with an acute episode of idiopathic TTP with respect to both PE alone and PE associated with standard doses of steroids. Identifying the best therapeutic approach to

the patients that fail to respond to this treatment, as well as a treatment for reducing recurrences in the subjects at risk, warrants further investigation.

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Table 1. Clinical and laboratory data at admission.

	Standard-dose methylprednisolone	High-dose methylprednisolone
Patients (n°)	30	30
Male/female (n°)	12/18	7/23
Age (years)	46 (37-61)	43 (34-52)
Fever (n°)	9	11
Neurological involvement (n°)	13	20
Haemoglobin (gr/dL)	9.4 (7.6-10.4)	8.1 (7.0-9.3)
Platelets (x10 ⁹ /L)	21 (6-24)	17 (7-22)
LDH (U/L)	3101 (955-2485)	2279 (965-2485)

Continuous variables are expressed as median (range)

Table 2. High-dose versus standard-dose methylprednisolone treatment in patients with idiopathic TTP. Comparison of treatment outcomes.

	Standard-dose methylprednisolone (n=30)	High-dose methylprednisolone (n=30)	Difference (95% CI)	P-value
	<i>Number of patients (%)</i>			
Failure to achieve good response* at day 9	13 (43.4)	7 (23.4)	-20 (-43 to +3)	0.17
Failure to achieve complete remission** at day 23	16 (53.4)	7 (23.4)	-30 (-53 to -6)	0.03
Death	4 (13.3)	1 (3.3)	-10 (-23 to +3)	0.35

* Platelet count more than $100 \times 10^9/L$ for two consecutive days without deterioration in the neurological status.

** Increase of platelets to more than $150 \times 10^9/L$, normalization of LDH value and improvement in neurological status.