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### Multi-center randomized open label phase II trial on three rituximab dosing schemes in immune thrombocytopenia patients

The overall short-term treatment efficacy of rituximab (R) in immune thrombocytopenia (ITP) is reported to be approximately 58%.<sup>1,2</sup> With four once-weekly 375 mg/m<sup>2</sup> doses, responses of 31% after two years,<sup>2</sup> and 21% after five years<sup>2</sup> can be expected with a median clinical improvement time of 10.5<sup>1</sup> months, and up to 49 months in other studies.<sup>3</sup> Since lower doses have comparable efficacy,<sup>4</sup> R remains an attractive second-line therapy especially in patients where splenectomy is contraindicated or should be delayed.<sup>1,3,5-8</sup>

However, there are no known response-modifying factors that can provide an optimal basis for choosing R and its dosing. Moreover, while numbers of ITP patients are limited, knowledge on these issues is mainly derived from (clustered) often small-sized and non-randomized studies.<sup>1-3,5,9</sup> Therefore, in order to, firstly, delineate the efficacy and safety of two alternative dosing strategies, and secondly, to study the R-response-modifying factors (RMF), the Dutch Hemato-Oncology Cooperative Group (HOVON) randomized 156 immune thrombocytopenia (ITP) patients between four once-weekly standard 375 mg/m<sup>2</sup> doses (arm A), a 2-weekly 375 mg/m<sup>2</sup> in early responding patients (arm B), and a 2-weekly 750 mg/m<sup>2</sup> regimen (arm C). In more detail, in arm B, when no early (at day 15) response was present or when response was lost within six weeks, another two once-weekly 375 mg/m<sup>2</sup> rituximab infusions were given.

Eligible patients needed to be 18 years of age or older and with an ITP relapse or refractoriness (at least 2 platelet counts less than 30x10<sup>9</sup>/L) and at least three weeks after high-dose corticosteroids (≥ 1mg/kg) before start of R (R start); further study details are available in the *Online Supplementary Appendix*. Complete (CR) good/partial (PR) and moderate (MR) response were defined as platelet counts of 150x10<sup>9</sup>/L or more and 50x10<sup>9</sup>/L or more on 2 consecutive occasions and a platelet count over 30x10<sup>9</sup>/L with at least twice the base-line count, respectively. Retrospectively, responses were also analyzed according to the International Working Group (IWG) ITP trial guidelines.<sup>10</sup> Relapse was defined as a further fall in platelet count to below 30x10<sup>9</sup>/L or below the 2-fold increase of base-line platelet count. Relapse-free survival (RFS), defined as time

from response until relapse, emergency treatment, or death, was analyzed using the actuarial Kaplan-Meier method. Patients still alive at the date of last contact were censored. The primary objective of this study was to evaluate the individual treatment arms as sufficiently promising (CR+ PR + MR > 50%) strategies<sup>11</sup> but not to compare the results between the treatment arms. All analyses were performed according to the intention-to-treat principle, irrespective of patients' compliance. Ineligible patients were excluded from all analyses. With 15 patients considered ineligible, and 3 patients who did not start with their assigned R treatment, 138 patients were evaluated for response as primary end point (Table 1).

Twelve patients (9%) went off treatment for various reasons. In 4 of these, this was related to R-attributed adverse events and toxicity; one patient in arm B experienced a life-threatening infection. Four patients received emergency treatments (for details see *Online Supplementary Table S1* and *Figure S1*). Weekly platelet counts were taken in all patients, up to ten weeks (day 71), after which responders were subsequently monitored monthly for at least 12 months. The median follow up of responding patients was 24 months (range 2-68; with 85% of responders monitored for >12 months).

As far as R-efficacy is concerned (Table 2), 68 (49 %) patients responded within ten weeks (19% CR, 20% PR, 11% MR); in 16 of these patients, the response even improved after ten weeks. Response results were similar: 52% for arm A (39%-65%; 90% confidence intervals), 47% for arm B (33%-60%), and 49% for arm C (37%-62%). Of 43 patients in arm B, 7 (16%) responded early and received two 375 mg/m<sup>2</sup> doses. Application of IWG

Table 1. Patients' characteristics.

	Arm A (n=46)	Arm B (n=43)	Arm C (n=49)
Dose received (mg/m <sup>2</sup> )	4x375	2 or 4x375	2x750
Male/female (%)	41/59	47/53	45/55
Age in years, median (range)	56 (18-77)	51 (18-80)	53 (17-82)
WHO 0/1/2/not reported (%)	85/11/-/4	91/9/-/-	82/16/2/-
Months between ITP diagnosis and rituximab start, median (range)	11.7 0.2-212	21.8 0.5-324	14.1 0.8-377
On stable or decreasing corticosteroids at R-start (%)	41	49	35
Splenectomized (%)	2	14	10
Base-line platelet count x10 <sup>9</sup> /L, median (range)	14 (3-36)	19 (2-38)	15 (1-30)

R: rituximab.

Table 2. Treatment outcomes.

Treatment outcome (%)	Arm A (n=46) 4x375 mg/m <sup>2</sup>	Arm B (n=43) 2 or 4x375 mg/m <sup>2</sup>	Arm C (n=49) 2x750 mg/m <sup>2</sup>
<b>Best response within 70 days</b>			
Total responders: n (%)	24 (52)	20 (47)	24 (49)
CR	10 (22)	7 (16) /5 after 2 doses	9 (18)
PR	9 (20)	8, (19)/2 after 2 doses	10 (20)
MR	5 (11)	5 (12) /1 after 2 doses	5 (10)
IWG total response	29 (63)	22 (51)	30(61)
IWG CR	19 (41)	12 (28)	15 (31)
IWG R	10 (22)	10 (23)	15 (31)
<b>Response period</b>			
Days between R start and initial response, median (range)	22 (3-66)	21 (1-70)	16 (5-59)
Response ≤ 14 days n (%)	9 (20)	7 (16)	12 (24)
% fast response of all responders	38 %	35 %	50%
Days between R start and best response, median (range)	52 (7-223)	49 (1-364)	48 (14-183)
DFS from CR at 2 years	89%	43%	76%
Observed relapses in fu	10	11	11
<b>Best response of initial responders from day 70</b>			
CR as best response in fu	13	9	11
PR as best response in fu	9	8	12
MR as best response in fu	1	3	1
Relapse *	1	0	0

One patient relapsed after response within 70 days.

response criteria defining CR as platelet counts above  $100 \times 10^9/L$  and 'Response' combining CR and PR (present in at least 2 measurements one week apart) led to even higher response rates: 63% (50%-75%), 59% (38%-64%), and 61% (48%-73%). Overall, responding patients showed a 72% RFS at one year and 58% at two years, and a median relapse-free survival of 29 months; comparisons between arms are, however, precluded by group patient numbers (Figure 1).

As response-modulating factors (RMF) studied throughout the 3 arms, early response (within 14 days vs. >14 days), showed more CRs within 70 days (18 of 28 vs. 8 of 40;  $P < 0.001$ ) and thereafter (19 of 28 vs. 14 of 40;  $P = 0.01$ ), but response duration and RFS were similar. Disease duration defined as time between initial diagnosis and start of R, was significantly shorter in patients reaching response (median 322 days; range 7-8964;  $P = 0.008$ ) and CR (237 days; range 29-7726;  $P = 0.042$ ) versus patients without response (median 783 days; range 23-11487). Vice versa, comparing 65 patients with ITP for less than a year, with 73 patients with ITP for more than a year, response (57% vs. 42%) and CR (27% vs. 22%) as well as 2-year RFS (66% vs. 46%;  $P = 0.06$ ) showed similar tendencies. No synergy was found between R and (still) having corticosteroids at study entry, and patient age was not associated with a higher probability to obtain a response ( $P = 0.25$ ) and RFS ( $P = 0.57$ ). The total response of 56% with 18 CR, 15 PR and 10 MR in female patients tended to be higher with 41% response ( $P = 0.08$ ), with 8 CR, 12 PR and 5 MR in males. Previous splenectomy was present in only 12 patients (with 1 CR, 1 PR and 3 MR) and could thus not be studied as RMF. In case of non-response or later relapse, patients often received other treatments. Of these, splenectomy was specifically studied with only 4 in 68 (6%) initially responding patients within one year after study initiation. In contrast, in the 70 non-responding patients, at least 15 patients (21%) underwent splenectomy within one year ( $P = 0.01$ ), while follow up data were not available for 17 of the non-responding patients.

Toxicities scored by the NCI Common Terminology Criteria for Adverse Events (CTCAE; v.3.0), as well as side effects, were clear and similar in all study arms (Table 3). In more detail, 22 patients (16%) experienced 23 CTCAE 3 or 4 events; of these, 10 patients (7%) with 10 CTC 3 and 4 events were recorded as SAEs. Another CTC 4 seizure should have been reported as SAE. As judged by more or

less close occurrence of events to R-administration, and the absence or presence of other causal factors, 6 of a total 11 events were considered to be probably or possibly treatment-related. Two events were judged to be definitely related to R-administration (5.7%); all events reversed without morbidity (*Online Supplementary Appendix*).

Our study first of all confirms that lower<sup>4</sup> but also more dense-dosed R are promising therapies for ITP patients. Interestingly, with 7 of 20 early responding patients receiving only two once-weekly 375 mg/m<sup>2</sup> doses, arm B did not lead to inferior results in response quality or RFS. The value of such a dose sparing strategy should, however, be confirmed by a randomized study comparing no or additional treatment in early responding patients. A second important issue is that response delays other treatments. In this respect, 15 of 63 non-responding patients underwent splenectomy in the first year after study entry, while this was needed in only 4 of 63 previously non-splenectomized responders. However, it remains to be determined whether R can eventually help avoid splenectomy.<sup>1,2,5</sup> Of the response-modulating factors studied in the pooled patients from all treatment arms, early response and female sex were associated with more frequent and better responses.<sup>12</sup> The latter, although non-significant, is in contrast to a recent meta-analysis which found male ITP patients to have a better 1-year response. Age is a complicated response modulator<sup>1</sup> because higher age is associated with longer disease duration and therapy resistance. In this light, we could indeed show that responding patients had shorter disease durations,<sup>3</sup> while response, CR and longer CR duration tended to be superior in patients with an ITP diagnosis of less than one year. In other studies, up-front corticosteroids combined with R<sup>12-14</sup> show synergy. We did not observe this effect, probably due to the fact that only corticosteroid-resistant patients were eligible for our study.

In conclusion, our detailed data can serve as a basis for future studies; for example, in which R is compared with other splenectomy-delaying approaches, such as TPO receptor agonists and splenectomy itself, and which include cost effectiveness and quality of life outcomes. Such studies might additionally generate the (immunological) predictors to help select the optimal ITP therapy and identify which patients would benefit most.<sup>8,16</sup>

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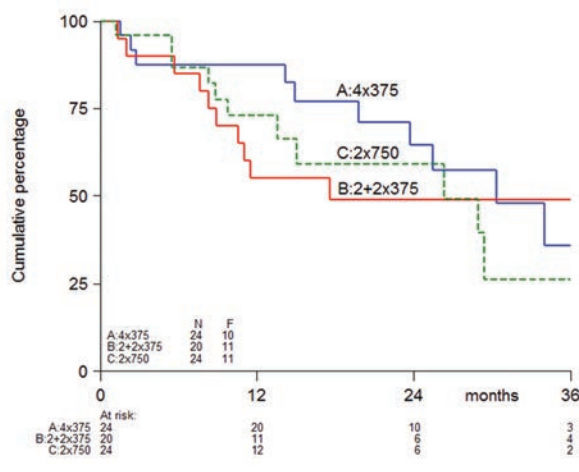


Figure 1. Relapse Free Survival (additional file).

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