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311. DISORDERS OF PLATELET NUMBER OR FUNCTION: POSTER III | NOVEMBER 29, 2018

Clinical and Morphologic Predictors of Outcome in a Multicenter Cohort of ITP Patients Treated with Trombopoietin Analogues

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Abstract

Background: The role of bone marrow response in patients with immune thrombocytopenia (ITP) has gained paramount importance since the last 10 years, with the demonstrations that marrow megakaryocytes (MGK) are unable to properly compensate platelets peripheral destruction. TPO receptor agonists (TPOa), namely romiplostim (ROMI) and eltrombopag (EPAG), by stimulating megakaryopoiesis are able to induce a response in 74% to 94% of cases in clinical trials. However, real world use of these drugs has shown frequent changes in individual dose requirement, the possibility of treatment discontinuation, and their effectiveness outside registered indications; moreover, nothing is known about predictors of response.

Aim: To evaluate clinical and morphologic predictors of response in a real world cohort of ITP patients treated with TPOa.

Methods: ITP patients treated with EPAG and ROMI from September 2009 to May 2018 at seven Italian Centers were evaluated. Clinical and hematologic parameters including treatment response and marrow characteristics were retrospectively collected.

Results: Table 1 shows baseline clinical and morphologic characteristics for the 86 cases enrolled, altogether and divided according to the TPOa used: patients were mainly middle-aged females

cases, and 58.1% of cases presented with bleeding, 22% of grade III-IV. All cases had received 1st line treatment with steroids and 43% at list a 2nd line among those listed in Tab1. Pre-TPOa marrow evalutation showed hypocellularity in 30.2% of cases, reticulinic fibrosis in 33.7%, a polyclonal lymphoid infiltrate in 43% (mostly mixed or T-cell), and reduced MGK in 4.7% of patients. Some dysplastic features were present in about 50% of cases, either dysmegakaryopoiesis (46.5%) or dyserythropoiesis (25.6%). Median time from diagnosis to TPOa was 2.4 years (0.1-28.8). Patients were treated for a median of 1.4 years (0.3-10.8), and ORR at 3 months and 9 months were 75.6% (CR 44.2 and PR 31.4%) and 65.1% (CR 36 and PR 29.1%), respectively. Response rates to EPAG and ROMI were comparable. Regarding predictors of response, bone marrow hypocellularity (40 NR vs 21% ORR, p=0.05) and megakaryocytopenia (33 vs 6%, p=0.06) were significantly more frequent among NRs. Other factors associated with poor response were dyserythropoiesis (58 vs 26%, p=0.04) and erythroid hyperplasia (18 vs 8%, p=0.03), and presence of a T cell infiltrate (66 vs 18.9%, p=0.03). Finally, NRs cases showed significantly lower neutrophil counts at baseline (1.9 vs $2.3x10^3$/mmc in ORR, p=0.01), and had been more frequently exposed to cyclosporine or azathioprine (50 vs 18% in ORR, p=0.01).

Fifty-five patients are still on treatment, whereas 31 (20 EPAG/11 ROMI) discontinued because of NR or relapse (17), adverse events or intolerance (2); of note, 12 patients with ORR discontinued the drug because of sustained CR, and 7 of them are still in remission. 14/65(21.5%) responding cases (10 EPAG/4 ROMI) lost the response after a median of 6.2 months (1.8-60) and were variably managed (3 splenectomized, 1 switched from ROMI to EPAG, 1 received danazol, 5 were re-treated with EPAG, and the remaining were managed with steroids and supportive treatment). Median RFS was 2.3 years (0.1-10), longer in patients without megakaryocytopenia (9.9+0.5 vs 4.1+0.6, p=0.06), dyserythropoiesis (mean 9.1+0.5 vs 4.9+0.7, p=0.2), and reticular fibrosis (9.6+0.5 vs 5.5+0.6, p=0.08). During EPAG treatment 7 grade adverse events occurred: 2 grade IV (1 stroke with PLT counts of about $30x10^3$/mmc, and 1 NSTEMI 1 month after EPAG discontinuation for sustained CR), 1 grade III pneumonia, and 4 grade I/II transaminase elevation. No events occurred under ROMI.

Conclusions: TPOa use in the real world setting confirms their reported efficacy, the option to switch and/or re-treat with either EPAG or ROMI, and the possibility to discontinue the drugs. The presence of hypocellularity and megakaryocytopenia, along with dysplastic features and of a lymphoid T cell infiltrate are associated with a reduced response to TPOa and a shorter RFS. Pre-treatment bone marrow evaluation may give hints to unravel the physiopathologic mechanisms underlying TPOa refractoriness.

Author Notes

Table 1. Clinical and laboratory characteristics of ITP patients divided according to TPOa treatment

	All cases N=86	Eltrombopag N=67	Romiplostim N=19
Clinical characteristics at diagnosis			
M N(%)	35(40.6)	26(38.8)	9(47.4)
F N(%)	51(59.4)	41(61.2)	10(52.6)
Median age years	63(6-87)	63(6-87)	61(20-79)
Median Plt x10^3/mmc	17.5(1-99)	21(1-99)	7(1-49)
Anti-PLT + N(%)	28(32.6)	24(35.8)	4(21)
Bleeding N(%)	50(58.1)	37(55.2)	13(68.4)
Grade I-II N	8 – 23	5 – 18	3 – 5
Grade III-IV N	16 – 3	12 – 2	4 – 1
Therapy lines			
Steroids N(CR/PR)	86(23/36)	67(15/29)	19(8/7)
Cyclosporin N(CR/PR)	16(3/3)	12(1/2)	4(2/1)
Azathioprine N(CR/PR)	5(0/3)	5(0/3)	0
Rituximab N(CR/PR)	19(2/8)	14(1/6)	5(1/2)
Splenectomy N(CR/PR)	20(9/5)	14(6/3)	6(3/2)
Danazol N(CR/PR)	8(1/3)	8(1/3)	0
Bone marrow features			
Median cellularity %	40 (8-90)	40(8-90)	47(30-80)
normal N(%)	39(45.3)	27(40.3)	12(63.1)
hyper N(%)	26(30.2)	21(31.3)	5(26.3)
hypo N(%)	18(20.9)	16(23.9)	2(10.5)
MF0 N(%)	57(66.3)	43(64.2)	14(73.7)
MF1 N(%)	29(33.7)	24(35.8)	5(26.3)
erythroid hyperplasiaN(%)	9(10.5)	7(10.4)	2(10.5)
dyserythropoiesis N(%)	22(25.6)	21(31.3)	1(5.3)
Median lymphoid infiltrate %	4(0-18)	1(0-4.5)	3(2-18)
absent N(%)	49(57)	34(50.7)	15(78.9)
mixed N(%)	12(14)	9(13.4)	3(15.8)
B N(%)	3(3.5)	2(3)	1(5.3)
T N(%)	14(16.3)	14(20.9)	0(0)
MGK normal N(%)	22(25.6)	15(22.4)	7(36.8)
increased N(%)	58(67.4)	46(68.6)	12(63.1)
reduced N(%)	4(4.7)	4(6)	0(0)
dysplastic N(%)	40(46.5)	33(49.2)	7(36.8)
Abnormal kariotype N(%)	2(2.3)	2(3)	0(0)
TPO analogue			
Time from diagnosis to TPO yrs	2.4(0.1-28.8)	2.4(0.1-28.8)	1.1(0.1-20)
3 months evaluations			
CR N(%)	38(44.2)	30(44.8)	8(42.1)
PR N(%)	27(31.4)	20(29.9)	7(36.8)
NR N(%)	15(17.4)	12(17.9)	3(15.8)
6 months evaluations			
CR N(%)	31(36)	24(35.8)	7(36.8)
PR N(%)	25(29.1)	20(29.9)	5(26.3)
NR N(%)	7(8)	6(9)	1(5.3)
Median RFS yrs	2.3(0.1-10)	2.08(0.1-10)	2.96 (0.2-8.6)

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Disclosures

Rossi: *MUNDIPHARMA:* Honoraria; *JANNSEN:* Other; *AMGEN:* Other: ADVISORY BOARD; *PFIZER:* Other: ADVISORY BOARD; *BMS:* Honoraria; *NOVARTIS:* Honoraria; *ROCHE:* Other

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CELGENE: Other: ADVISORY BOARD; *JAZZ:* Other: ADVISORY BOARD; *SANOFI:* Other: ADVISORY BOARD; *GILEAD:* Other: ADVISORY BOARD; *SANDOZ:* Honoraria.

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Author notes

* Asterisk with author names denotes non-ASH members.

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