Prospective Evaluation of the First Option, Second-Line Therapy in Childhood Chronic Immune Thrombocytopenia: Splenectomy or Immunomodulation

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Objective To describe 4 subgroups of pediatric patients treated with splenectomy, hydroxychloroquine, azathioprine, or rituximab as the first-option, second-line treatment for chronic immune thrombocytopenia.

Study design Selection of patients with chronic immune thrombocytopenia from the French national prospective cohort of pediatric autoimmune cytopenia OBS'CEREVANCE and VIGICAIRE study, treated by splenectomy, hydroxychloroquine, azathioprine, or rituximab as a first second-line treatment.

Results For 137 patients, treated between 1989 and 2016, the median follow-up after diagnosis and after treatment initiation was 8.5 (2.8-26.4) years and 4.7 (1.1-25.1) years, respectively. Median age at diagnosis and at initiation of treatment were 9 (0.7; 16) and 12 (2; 18.1) years, respectively without significant difference between subgroups. For the whole cohort, 24-month event-free survival was 62% (95% CI 55; 71). It was 85% (95% CI 77; 95) for the 56 patients treated with splenectomy, 60% (95% CI 44; 84) for the 23 patients treated with rituximab, 46% (95% CI 30; 71) for the 24 patients treated with azathioprine, and 37% (95% CI 24; 59) for the 34 patients treated with hydroxychloroquine (log-rank $P < .0001$). For the splenectomy subgroup, being older than 10 years at splenectomy tended to improve event-free survival ($P = .05$). Female teenagers with antinuclear antibody positivity benefited from hydroxychloroquine therapy.

Conclusions This national study, limiting pitfalls in the analysis of the effects of second-line therapies, showed that splenectomy remains the treatment associated with the better response at 24 months. *(J Pediatr 2021;231:223-30)*.

Immune thrombocytopenia (ITP) is a potentially life-threatening autoimmune disease. In approximately 20% of patients, it has a chronic course of >12 months (chronic ITP [cITP]). Second-line treatments are necessary for a subgroup of patients to prevent severe hemorrhaging and significant morbidity. The management of children with cITP has been described without any comparison: for 81 patients with numerous medications[1] and in 58 patients with splenectomy.[2] In our French study, 55% of 392 children with cITP diagnosed from 1990 to 2014 received second-line treatments.[3]

Common first-line therapies are steroids and intravenous immunoglobulins (IVIg). Clinically symptomatic children who suffer disease relapse or first-line treatment failure receive second-line therapies, splenectomy, or various drugs. Most of the latter have not been approved by regulatory authorities for treatment

AE	Adverse event
ANA	Antinuclear antibody
cITP	Chronic ITP
EFS	Event-free survival
ITP	Immune thrombocytopenia
IVIg	Intravenous immunoglobulins
SLE	Systemic lupus erythematosus

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of ITP in children, but they are nonetheless prescribed in cITP because of their demonstrated efficacy in other autoimmune diseases or in adults.

Splenectomy yields a high sustainable response rate in children and adults with cITP.[4] However, the risk of infections and thrombosis limit its use, and its decreasing use has been reported by several authors including our group.[3-5]

Rituximab, an anti-CD20 molecule, is a first-option second-line agent with evidence-based data on its effectiveness in childhood ITP, allowing response rates of 30%-68%[6-8]; however, response seems to fade over time.[9-11]

Azathioprine, a purine analogue inhibitor of lymphocyte proliferation, is the only second-line drug authorized in France to treat children with ITP. A retrospective adult series showed a response rate of >50% persistent for 12 months in majority of patients,[12,13] but there are no data on its use in pediatric cITP.

Hydroxychloroquine, an immunomodulatory agent, is used mainly in patients with systemic lupus erythematosus (SLE). In adults, as in children, 10%-15% of ITP cases are associated with SLE biomarkers.[14,15] In adults with ITP and positive antinuclear antibody (ANA), a slow long-term response was obtained in 60% of patients.[15] In children, the benefit was enhanced when ITP is associated with SLE biomarkers.[16]

The present study aims to describe in a prospective real-life care setting, 4 subgroups of patients with cITP, treated with the 4 most frequently used first-option second-line treatments: splenectomy, hydroxychloroquine, azathioprine, and rituximab.

Methods

Since 2004, French children under 18 years old with autoimmune cytopenia (cITP with a >12 months course, autoimmune hemolytic anemia, or Evans syndrome) have been included in a national prospective cohort OBS'CEREVANCE.[17,18] In this observational cohort, in clinical practice, treatments are given at the free choice of the clinician, according to national and international guidelines and to the clinical context of the patient. Evaluation of the patients was performed every 3 months during the follow-up. Written informed consent is obtained. All relevant data are prospectively collected and integrated into a specific database, validated by the French authorities (Commission for Information Technology and Civil Liberties, November 9, 2009; 1396823V0). The cohort was analyzed on October 31, 2017.

VIGICAIRE was a study sponsored by Agence Nationale de Sécurité du Médicament (2014-2017) that made use of this robust observational national database, with a methodological center and a pharmacovigilance unit providing a web-VIGINOM interface for data collection. The aim was to describe the benefit–risk balance at 24 months of the main medications prescribed as first-option second-line treatment. The subgroup of 81 children included in VIGICAIRE for cITP diagnosed between May 1996 and October 2014 and treated with rituximab, hydroxychloroquine, or azathioprine was analyzed. The same methodology was used to analyze the subgroup of 56 patients included in OBS'CEREVANCE with cITP diagnosed between January 1987 and March 2014 with splenectomy as first second-line treatment. None of those patients participated in other academic or industrial clinical trials during the period of this study.

Definitions

Inclusion criteria were patients between 1 and 18 years old treated after IVIg and/or steroids with rituximab, hydroxychloroquine, azathioprine, or splenectomy for cITP. Exclusion criteria were patients with previously known SLE[19] or genetic primary immune deficiency, patients receiving any previous immunosuppressive drugs, and patients treated concomitantly with 2 immunosuppressive drugs. Clinical bleeding severity was graded on a scale from 0 to 4 in 4 different sites (overall, oral, epistaxis, and skin) on the basis of history during the previous 24 hours and physical examination (Buchanan score).[20] ITP severity was estimated on a combination of a Buchanan score ≥3, platelet count <10 G/L, or a subjective perception of altered quality of life. Treatment efficacy was assessed by the absence of events: the need to introduce further second-line treatment or to discontinue treatment for toxicity, the absence of complete remission (platelet count >100 G/L), the lack of compliance, or patient death. Treatment tolerance was described and recorded at each evaluation every 3 months for the first 24 months. Adverse events (AEs) were graded according to Common Terminology Criteria for Adverse Events v 4.0 scale.

Statistical Analyses

Qualitative variables are presented as numbers and percentages, and quantitative variables as medians and minimum–maximum values. The distribution of categorical variables was compared by χ^2 test or Fisher exact test. Continuous variables were analyzed using Kruskal-Wallis test. Event-free survival (EFS) was analyzed by Kaplan-Meyer curves from the date of initiation of the first second-line therapy to the date of the event. Patients were censored at the date of last follow-up if they had not presented an event. Patient subgroups were compared using log-rank test. The factors associated with survival without events were studied using univariate Cox regression for sex, age at ITP diagnosis, significant ANA positivity (>1/160), and age at initiation of second-line treatment. All statistical analyses were performed using R software (version 3.3.2, R Foundation for Statistical Computing). A P value of <.05 was considered to indicate statistical significance.

Results

Selection of Patients

Between September 1989 and June 2016, 10% (137 of 1316) of patients with cITP included in OBS'CEREVANCE had

started 1 of the 4 second-line treatments. The median follow-up after diagnosis was 8.5 years (2.8-26.4). In 95% of the patients, treatment was administered as monotherapy for >3 months. The second-line treatments were distributed as follows: splenectomy (n = 56), hydroxychloroquine (n = 34), azathioprine (n = 24), and rituximab (n = 23). Only 5 patients had a follow-up of <2 years. The median follow-up after treatment cessation was 4.7 years (0.1–25.1).

Description of the Population

Sixty-nine female patients were included (Table I). In the hydroxychloroquine and azathioprine subgroups, the sex ratio (F/M) was >1. The median age of patients at ITP diagnosis was 9 years (0.6; 16) without significant difference between subgroups. Nine of the 137 patients (6.5%) had developed manifestations leading to the diagnosis of secondary ITP. Eight patients had SLE (hydroxychloroquine subgroup [n = 4], rituximab subgroup [n = 2], splenectomy subgroup [n = 2]), and 1 patient in the azathioprine subgroup was diagnosed with a primary immune deficiency (gain-of-function STAT3 mutation). Seven patients (5.1%) developed Evans syndrome after median delay of 5.3 years (2.5-10.0) from diagnosis.

The median delay between diagnosis and second-line treatment initiation was 28 months (12; 160.1). The median age of the patients at treatment initiation was 12 years (2; 18.1), with a trend toward a higher median age (13.3 years) in hydroxychloroquine subgroup. At time of treatment initiation, 13% of the patients had a Buchanan score ≥3, and 27% and 66% of patients had platelet counts of <10 G/L and <30 G/L respectively.

Treatment Procedure

Treatment were implemented according to French guidelines (Table II).[21] For 45 of 56 patients treated with splenectomy for whom information was available, laparotomy was proposed in 5, and laparoscopy in 40 patients, with conversion to laparotomy in 9 patients. For all patients, prior vaccines were made according to the guidelines. Sixteen patients had isotopic studies: the platelet destruction was purely or predominantly splenic in 12 cases. The 34 patients treated with hydroxychloroquine received a median dose of 6.1 (2.5-16.0) mg/kg/day for a median duration of 13.6 (0.1-136.0) months (<3 months for 6 patients, <6 months for 12 patients). For 14 of them, treatment was still ongoing at latest news. The 24 patients treated with azathioprine received a median dose of 1.8 (1.0-3.0) mg/kg/day for a median duration of 11.8 (1.4-101.7) months (<3 months for 4 patients). Treatment was still ongoing at latest news for 9 of them. The 23 patients treated with rituximab received a weekly dose of 375 mg/m^2 for less than 3 doses (n = 6), 4 doses (n = 14), 5 doses (n = 1), and 8 doses (n = 1). One patient (15.8 years of age) with a body surface area of 1.72 m^2 received 1000 mg once.

Efficacy at 24 Months

In this observational prospective study, a new composite endpoint was used to describe events and EFS. For the whole cohort (Table II), the 24-month EFS was 62% (95% CI 55;

Table I. Description of the population at second-line treatment initiation

	Whole cohort n = 137	Splenectomy n = 56	Hydroxychloroquine n = 34	Azathioprine n = 24	Rituximab n = 23	*P* value
Consanguinity, n (%)*	2/60 (3%)	0/16 (0%)	0/15 (0%)	1/11 (9%)	1/18 (5%)	-
Immune manifestations in first degree relatives, n (%)*	19/104 (18%)	6/38 (16%)	5/26 (19%)	4/19 (21%)	4/21 (19%)	NS
Sex ratio (female/male)	1.0 (69/68)	0.9 (26/30)	1.4 (20/14)	1.2 (13/11)	0.7 (10/13)	NS
Primary ITP, n (%)	128/137 (93%)	54/56 (96%)	30/34 (88%)	23/24 (96%)	21/23 (91%)	NS
Number of patients with ANA >1/160*	38/55	8/11	18/25	3/7	9/12	NS
Median age at first cytopenia, y (min, max)	9.0 (0.7, 16.0)	8.4 (0.7, 14.3)	10.2 (1.0, 16.0)	9.6 (0.7, 15.4)	9.1 (0.7, 15.3)	NS
Median age at treatment initiation, y (min, max)	12.0 (2.0, 18.1)	11.5 (2.0, 18.1)	13.3 (3.9, 17.7)	12.4 (2.4, 16.8)	11.8 (3.4, 17.7)	NS
Median delay from first cytopenia to treatment initiation, m (min, max)	28.4 (12.0, 160.1)	35.7 (12.0, 160.1)	30.6 (13.5, 130.1)	22.4 (12.0, 132.6)	26.3 (13.1, 110.4)	NS
Status of ITP at initiation of treatment						
Score Buchanan median (min, max)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)	1 (0-3)	-
Number of patients with Buchanan score ≥3	13/96	1/17	4/32	3/24	5/23	-
Median platelets count (min, max)	18.0 (1.0, 426.0)	24.5 (3.0, 230.0)	20.0 (1.0-174.0)	16.5 (1.0-128.0)	10.5 (1.0, 426.0)	<.001
Number of patients with platelet count <30 G/L	76/115 (66%)	22/36 (61%)	20/33 (61%)	16/24 (67%)	18/22 (82%)	NS
Number of patients with platelet count <10 G/L	32/115 (28%)	7/36 (19%)	9/33 (27%)	6/24 (25%)	10/22 (45%)	NS

NS, no statistical significance.
*Denominator: number of patients with available data.

Table II. Efficiency and tolerance of the main second-line treatments

	Whole cohort n = 137	Splenectomy n = 56	Hydroxychloroquine n = 34	Azathioprine n = 24	Rituximab n = 23
Efficiency					
Number of patients without Buchanan ≥3 in the first 24 mo, n (%)	93/136 (68%)	49/56 (87%)	21/33 (64%)	11/24 (46%)	12/22 (54%)
Number of patients with no further second-line in the first 24 mo, n (%)	95/135 (70%)	48/56 (86%)	19/32 (64%)	14/24 (58%)	14/23 (61%)
Number of patients with no IVIG/steroid pulses in the first 24 mo, n (%)	70/132 (53%)	43/53 (81%)	8/33 (24%)	9/24 (37%)	10/23 (43%)
Reason for treatment discontinuation within the first 24 mo, n					
AE, n	35	NA	20	14	1
Lack of compliance, n	2	NA	1	0	1
Non response without any further second-line, n	3	NA	2	1	NA
Nonresponse with further second-line, n	8	NA	6	2	NA
Response, n	20	NA	10	10	NA
Status of ITP at 24 mo for patients with no further second-line?	2	NA	1	1	NA
Score Buchanan median (min, max)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-2)
Number of patients with Buchanan score ≥ 3	0	0	0	0	0
Median platelet count (min, max) G/L	95 (4, 559)	184 (1.8, 559)	70 (11, 245)	70 (4, 300)	37 (8, 290)
Number of patients with platelet count <30 G/L	14/70 (20%)	5/32 (16%)	2/15 (13%)	3/12 (25%)	4/11 (36%)
Number of patients with platelet count <10 G/L	5/70 (7%)	2/32 (6%)	0/15 (0%)	1/12 (8%)	2/11 (18%)
Tolerance					
Number of patients with severe AE grade ≥3 in the first 24 mo, n	6/137	0/56	3/34	2/24	1/23
Number of infectious AE grade ≥ 3 in the first 24 mo, n	3/137	0/56	0/34	3/24	0/23
Deaths, n	1/137	1/56	0/34	0/24	0/23

71). EFS was 85% (95% CI 77; 95), 60% (95% CI 44; 84), 46% (95% CI 30; 71), and 37% (95% CI 24; 59), respectively, in the splenectomy, rituximab, azathioprine, and hydroxychloroquine subgroups (Figure; log-rank $P < .0001$). Among the 12 patients treated with splenectomy with pure or predominant splenic destruction, the 24-month EFS was 83% (95% CI 64; 100) vs 75% (95% CI 65; 100) for others ($P = .8$). The EFS of patients treated with splenectomy was significantly better than that of patients treated with any of the drug regimens: 85% (95% CI 77; 96) vs 47% (95% CI 37; 59) ($P < .0001$). There was no significant difference between the latter subgroups, even if rituximab allowed reaching a 60% 24-month EFS. During the 24 months of follow-up after initiation of second-line treatment, 70% of patients did not receive any further second-line, and 53% did not need IVIg or corticosteroid pulses. Interestingly, majority of female patients older than 10 years at either hydroxychloroquine (12 of 18) or rituximab (3 of 5) initiation did not require further second-line treatment.

The 95 patients without further second-line treatment during the 24 months of follow-up had a median Buchanan score of 0 (95% CI 0; 1) and a median platelet count of 95 G/L (4; 559).

When predictive factors associated with response were analyzed, none significantly influenced EFS in hydroxychloroquine, azathioprine, and rituximab subgroups (Table III). For splenectomy, being >10 years of age at splenectomy tended to improve EFS ($P = .05$).

Tolerance at 24 Months

During follow-up, 4.4% of patients (n = 6) presented with 7 grade 3 or 4 AEs, which rapidly resolved; however, in 2 patients, treatment was discontinued. Three patients were in the hydroxychloroquine subgroup. One patient had an accidental overdose requiring gastric evacuation and 48 hours of treatment discontinuation. The second patient had a transient significant decrease in visual acuity; it rapidly resolved, but treatment was ended. The third patient suffered depression and anorexia requiring hospitalization, but the incident was not considered directly related to treatment. Two patients were in the azathioprine subgroup. One patient had *Salmonella typhimurium* gastroenteritis that required brief hospitalization. The other patient had acute otitis media and subsequent alteration of general condition with febrile neutropenia that required brief hospitalization. The sixth patient, treated with rituximab, developed an anaphylactic grade 3 reaction a few minutes after beginning of the first infusion; treatment was stopped. None of the 23 patients treated with rituximab experienced hypogammaglobulinemia after the first year of follow-up.

During the total follow-up period, a 28-year-old male patient died of severe sepsis 24.3 years after ITP diagnosis. At the time of his death, after a high burden of

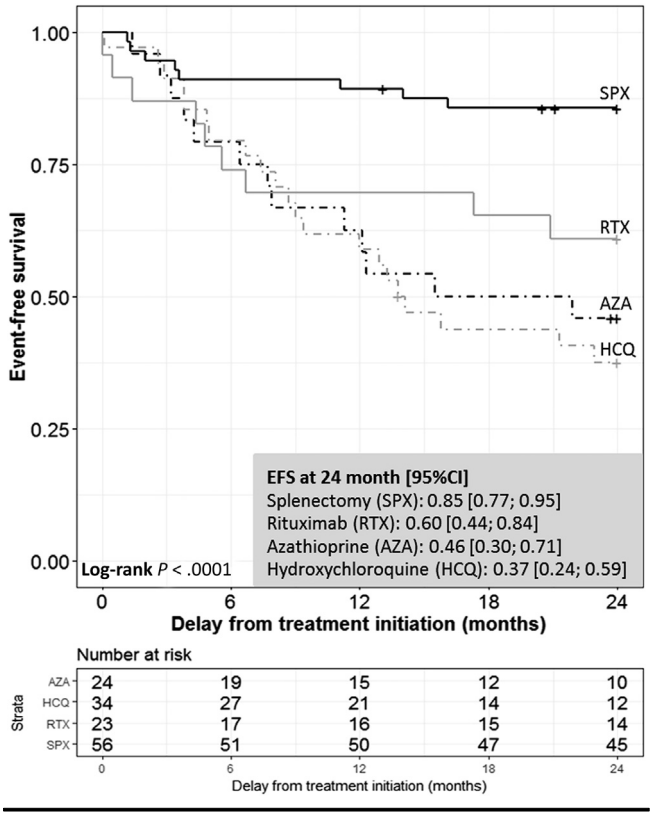

Figure. Twenty-four month-event free survival for the 4 second-line treatments.

Table III. Factors influencing the event-free survival for the 4 second-line treatments

	Univariate analysis		
	Relative risk	95% CI	*P*
Splenectomy (n = 56)			
Sex, male vs female	0.91	[0.23; 3.63]	.89
Age at ITP diagnosis (>10 y, <10 y)	0.26	[0.03; 2.11]	.20
Age at initiation of the second-line (>10 y, <10 y)	0.24	[0.06; 0.98]	**.05**
ANA ≥1/160	-	-	-
Hydroxychloroquine (n = 34)			
Sex, male vs female	1.75	[0.74; 4.14]	.20
Age at ITP diagnosis (>10 y, <10 y)	0.70	[0.30; 1.66]	.42
Age at initiation of the second-line (>10 y, <10 y)	0.45	[0.17; 1.18]	.10
ANA ≥1/160	1.70	[0.47; 6.09]	.42
Azathioprine (n = 24)			
Sex, male vs female	0.95	[0.32; 2.84]	.93
Age at ITP diagnosis (>10 y, <10 y)	0.44	[0.12; 1.59]	.21
Age at initiation of the second-line (>10 y, <10 y)	0.73	[0.25; 2.17]	.57
ANA ≥1/160	1.0	[0.17; 6.01]	.99
Rituximab (n = 23)			
Sex, male vs female	0.51	[0.14; 1.90]	.31
Age at ITP diagnosis (>10 y, <10 y)	1.03	[0.28; 3.85]	.96
Age at initiation of the second-line (>10 y, <10 y)	0.33	[0.09; 1.25]	.10
ANA ≥1/160	0.42	[0.07; 2.55]	.35

Bold value represent statistically significant value.

immunosuppressive treatments received for Evans syndrome, a primary immune deficiency was suspected but not identified.

Discussion

This national study of the use in real-life care of splenectomy or 3 immunomodulatory drugs in first-option second-line treatment of pediatric cITP, before the era of TPO-receptor agonists, established a short term favorable benefit–risk balance in the first 2 years, assuming that a careful preventive follow-up is maintained all life-long. Difficulties in obtaining a lasting comprehensive response in pediatric patients with cITP remain at the foreground.

Although our study was not a randomized controlled trial, this large prospective cohort of patients with cITP previously treated only by first-line therapies is highly informative concerning the use of the main second-line treatments. The descriptive data show that the decision to treat, in real life, cannot be restricted to clinical or hematological criteria for severity and probably involves subjective criteria as patient, parent, or clinicians anxiety. The OBS'CEREVANCE cohort and the VIGICAIRE study promote an innovative methodology and support the referral centers and regulatory authorities in France in carrying out their respective duties. Unlike guidelines for ITP trials and majority of series,[22] in this study, the response to treatment was evaluated using a new composite endpoint based on our opinion that a single platelet count, with no accompanying clinical data and modified by multiple ongoing treatments, does not reflect the exact status of disease.

The clinical characteristics of the four subgroups, comprising 137 patients with cITP, were comparable with each other and to cohorts in previous studies.[1,23,24] However, among the 24 children treated with hydroxychloroquine, female patients predominated, the age at initial diagnosis of ITP was slightly higher, and 16% of those patients developed authenticated SLE within 2 years representing a subgroup of pediatric SLE with hematological presentation.

In our cohort, historically, the main first second-line treatments included splenectomy, hydroxychloroquine, azathioprine, and rituximab. According to the guidelines in use in France during the study period, TPO-receptor agonists, expensive, with the sole eltrombopag licensed since 2016, were delayed as third or fourth-line treatment.[25]

Among the patients treated with splenectomy, 89% had a laparoscopy, now recognized as a suitable procedure in this context.[26] Only 19% of patients had an isotopic study before splenectomy. The predictive value of splenectomy in terms of its efficacy in patients with splenic sequestration is well known, but limited availability and the technical aspects of the procedure restrict its use.[27-29] When patients were treated with rituximab, the guidelines were most of the time followed: 4 weekly doses of 375 mg/m^2.[6,9] Only 1 patient received a dose of 1g, which has been shown to be an effective and safe alternative.[30] For oral drugs, the optimal dose and

treatment duration in children have yet to be definitively determined. Hydroxychloroquine was initiated in our patients at a median dose of 6.1 mg/kg/day, but the dose ranged from 2.5 to 16 mg/kg/day.[21] The median duration was 13.6 months and was consistent with our preliminary experience, which showed increasing percentages of response after 6, 12, and 24 months.[16] In our study, azathioprine was administered for a median duration of 11.4 months, without data establishing the optimal dose. In the sole available series, of 53 adults, the median duration of treatment was 18 months, and the median time to achieve a response was 4 months.[12] We believe that drug failure in pediatric cITP should not be assessed before 4-6 months and that a minimal duration of 18-24 months in case of response is reasonable before a slow decrease in the dose.

The 24-month EFS was 68% (95% CI 55; 71) for the entire cohort, splenectomy exhibiting clear superiority with an EFS of 85% (95% CI 77; 95). Our observational endpoint of "further second-line-sparing treatment" complicated a direct comparison of the present results with those of previous studies, in which response rates were reported as isolated platelet counts possibly influenced by concomitant treatments. In cITP, because relapses may occur several years after diagnosis, a long-term period of more than 24 months to evaluate the efficacy of treatments seems mandatory.

Splenectomy remains the optimal strategy. Previous retrospective studies also emphasized the long-term duration of apparent cure after splenectomy, with various endpoints.[2,31] However, we previously reported a 5-year relapse free survival of 51% in 78 children,[32] prompting to continue long-term follow-up for those patients.

Concerning rituximab, previous studies showed that an older age at diagnosis (9.7 years)[33] and/or at treatment initiation (12.7 years)[11] and female sex[11,34] are predictive of a favorable response. Our subgroup of patients had a median age of 9.1 years at initial diagnosis and the sex ratio (F/M) was 0.7; this latter point could explain the 24-month EFS, which was only 60%.

We report satisfactory results in use of azathioprine to treat childhood cITP, oral, well-tolerated, licensed, and inexpensive treatment, with available pharmacologic drug monitoring. The 24-month EFS was 46% and 58% of patients did not require further second-line treatment. The previous study of adult cITP showed a higher response to azathioprine in female patients,[12] and in our study, the majority of patients of this subgroup were female.

The results achieved with hydroxychloroquine were disappointing, as the 24-month EFS was only 37%. This can perhaps be explained by the choice of patients (41% were male; 28% had no significant ANA positivity >1/160), by the treatment short duration (35% were treated for <6 months), or by the absence of pharmacologic drug monitoring to optimize it. A positive response to hydroxychloroquine has been linked to SLE and the presence of autoantibodies (ANA or anti-thyroglobulin)[15] and is better observed after 4-6 months.[15,16] Finally, 6% of our hydroxychloroquine-treated patients had poor compliance, as also observed in SLE patients.[35]

The tolerance of the treatments at 24 months were good, with only 4.3% of patients suffering a grade 3 or 4 AE. Concerning rituximab, only 1 patient presented an anaphylactic reaction, which is in line with data reported in a systematic review with 2 reactions among 91 patients[9]; no patients had hypogammaglobulinemia in our study which could be explained by the exclusion of common variable immunodeficiency and the absence of concomitant treatment with dexamethasone which are 2 known risk factors in post rituximab hypogammaglobulinemia.[11,36] One of our patients treated with hydroxychloroquine (4%) had a decrease in visual acuity, a well-known AE; this risk increases with increasing treatment duration. We, therefore, recommend yearly ophthalmologic follow-up in children.[37] None of our patients treated with azathioprine discontinued therapy because of an AE. Two patients had an infectious intercurrent event. One of them was associated with a transient neutropenia, which could be viral or linked to *TPMT* polymorphism. Neutropenia associated with azathioprine have been already described and linked to *TPMT* polymorphisms.[38] A systematic screening of *TMPT* polymorphisms proposed before azathioprine initiation to tailor the doses.[38] Concerning splenectomy, no patient experienced severe or recurrent infection nor thrombosis during the 24 months follow-up, in accordance with data published by Kuhne et al with only 7 sepsis among 153 patients in a similar follow-up.[39] However, the cumulative prevalence of sepsis and thrombosis grows with age and can occur up to 20 years after the procedure. Adequate antibiotic prophylaxis, immunizations, and patient education are to be maintained all life-long.[4] The sole death in this study was that of a patient who died 24 years after ITP diagnosis and who underwent splenectomy as the first of numerous second-line treatments. He developed Evans syndrome, which underlines the specificity and severity of multilineage autoimmune cytopenia, linked to genetic background and heavy treatments.[17,40]

This national study analyzing 4 second-line therapies in children with cITP demonstrated that splenectomy remains associated with the better prognosis at 24 months. Our results also pointed the pitfalls in the analysis of the effects of second-line drug-based treatments.

Because cITP in children is a heterogeneous disease, the first step is the use of validated criteria to choose a targeted treatment. In addition, methodologically correct studies should be conducted to define the underlying context for each patient and the predictive clinical parameters or immunologic biomarkers associated with a positive response. For example, female teenagers with ANA positivity are a specific subgroup of patients that benefit from hydroxychloroquine therapy.

Ongoing collaborative studies with homogeneous guidelines regarding optimal doses, duration, and pharmacologic monitoring of oral second-line treatments, will allow

describing short- and long-term follow-up of those rare patients. ■

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50 Years Ago in *THE JOURNAL OF PEDIATRICS*

An Early Description of Persistent Pulmonary Hypertension of the Newborn

Siassi B, Goldberg SJ, Emmanouilides GC, Higashino SM, Lewis E. Persistent Pulmonary Vascular Obstruction in Newborn Infants. J Pediatr 1971;78:610-5.

In 1971, Siassi et al described 5 full-term infants with delayed transition from fetal to neonatal circulation. All developed cyanosis and tachypnea soon after birth without grunting or retractions. On radiographs, findings of parenchymal lung disease such as granularity and air bronchograms were notably absent. An electrocardiogram and diagnostic cardiac catheterization were performed to exclude congenital heart disease. These tests showed a structurally normal cardiac anatomy with right ventricular hypertrophy, right-to-left shunting at the ductus arteriosus, and a pulmonary artery blood pressure equal to or greater than the aortic blood pressure. All infants received supplemental oxygen, and 4 of the 5 survived to discharge. One died on the third day, and autopsy of this infant showed smooth muscle hypertrophy of pulmonary arterioles.

In the intervening 50 years, the diagnosis and treatment of persistent pulmonary hypertension of the newborn (PPHN) has seen a dramatic evolution. Although most cases of PPHN are mild, severe PPHN at the time of this publication was commonly lethal, as it was in one of the infants described in the series. In the 1980s, extracorporeal membranous oxygenation was shown to be effective at decreasing mortality in severe PPHN.[1] In 1999, the US Food and Drug Administration approved the use of inhaled nitric oxide for PPHN, and it has since become the mainstay of therapy, sparing most patients from extracorporeal membranous oxygenation.[2] Pulse oximetry and echocardiography, noninvasive alternatives to cardiac catheterization, are now the standard of care for the evaluation of this disease. The rapid advancement in the treatment of PPHN has paralleled the progress of research in the field of pulmonary vascular biology. Hopefully, continued work in this field will lead to similar improvements in the outcomes of patients affected by other forms of neonatal pulmonary vascular disease.

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