Outcome of High-risk Langerhans Cell Histiocytosis (LCH) in Egyptian Children, Does Intermediate-dose Methotrexate Improve the Outcome?

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Summary: High-risk multisystem organ (RO+) Langerhans cell histiocytosis (LCH) has the least survival. We present the outcome of RO+ LCH in a pediatric single center. Fifty RO+ LCH patients, treated between 07/2007 and 07/2015, were retrospectively analyzed. Induction vinblastine (VBL) and prednisone (PRED) with intermediate-dose methotrexate (idMTX) was adopted until 2012 (n = 20) wherein idMTX was omitted (n = 30). The 3-year overall survival (OS) of MTX and non-MTX groups was 75% and 63%, respectively, $P = 0.537$, while the event-free survival (EFS) was 36.9% and 13.2%, respectively, $P = 0.005$. At week 12 of induction, "better status" was obtained in 80% of those receiving MTX, and 55% of those who were not. The statistically significant factors associated with both poor OS and EFS were trihemopoietic cytopenias, hepatic dysfunction, tri RO+ combination, and single induction. The factors associated with disease progression (DP) on induction were trihemopoietic cytopenias, hepatic dysfunction, and lack of idMTX, while those for disease reactivations (REA), the season of autumn/winter, lung disease, male sex, and idMTX were the associated factors. The 1-year OS was remarkably affected with the occurrence of DP versus REA versus none, wherein it was 47%, 93%, and 95%, respectively, $P = 0.001$. In conclusion, idMTX is associated with better EFS. DP on induction remains of dismal prognosis in relation to disease REA afterwards. Risk stratification should highlight the role of trihemopoietic cytopenias, hepatic dysfunction, tri RO+, central nervous system risk site, and lung association.

Key Words: intermediate-dose methotrexate, high-risk LCH, disease progression, reactivation, survival

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Langerhans cell histiocytosis (LCH) is a rare clonal disease characterized by the accumulation of abnormal dendritic cells in different organs and systems.[1] Multisystem disease patients, including those with bones +/− central nervous system (CNS) risk sites, skin, lymph nodes and others, benefit from vinblastine (VBL) and prednisone (PRED).[2] However, those patients with high-risk organ (RO +) involvement (hemopoietic system, liver and spleen +/− lungs) have the highest mortality, [1,3,4] and those who present with failure of the first-line treatment show a very low survival rate reaching 30%.[5–7] For RO^+ patients, intermediate-dose methotrexate (idMTX) that was added in induction to VBL PRED in LCH III (Trial No. NCT00276757) has proved no significant role.[8]

The aim of the current study was to assess the outcome for RO+ LCH and to highlight the effect of omitting idMTX in a single pediatric Egyptian center.

PATIENTS AND METHODS

Study Population

The medical records of LCH patients were reviewed and retrospectively analyzed. Two hundred seventeen patients were treated at a single center, Children Cancer Hospital—Egypt 57357, between July 2007 and July 2015. Until the beginning of 2012, RO+ patients were used to receiving an induction including idMTX. This was omitted afterwards, for succeeding patients, according to the preliminary results of the Histiocytosis Society, doubting its beneficial effect.[8] Fifty consecutive patients (RO+) were included in the study for analysis. Their charts were reviewed after the approval of the scientific and medical advisory committee for demography, response to induction therapy, disease reactivation (REA), and survival according to the LCH III protocol outline.[8]

Diagnosis

All patients were evaluated with comprehensive physical examination, complete blood count, liver and kidney function tests, serum electrolytes, phosphorus, and calcium, as well as urinary examination for osmolality. Radiologic examination included a minimum of skeletal survey and chest x-ray, and abdominal sonogram with further specific computed tomography, or magnetic resonance imaging according to the affected areas. Diagnosis was confirmed by histopathologic examination showing CD1a or CD207 (langerin) with or without S100, according to the Histiocytosis Society criteria.[9]

Disease Stratification

High-risk patients (RO+) at diagnosis were stratified when any of the Multisystem "RISK" organs (RO+) involvement was confirmed according to Lahey criteria:[10] hematopoietic system with cytopenias (mono, bi, tricytopenias) defined as anemia (hemoglobin: <100 g/L, infants: <90 g/L) and/or leucopenia (white blood cell count: <4.0×109 /L) and/or thrombocytopenia (platelets: <100×109 /L). Hepatomegaly was described as a size of at least 3 cm below the costal margin and/or hepatic dysfunction (hypoproteinemia, hypoalbuminemia, hyperbilirubinemia, and/or increased liver enzymes). Splenomegaly was described as at least 2 cm below

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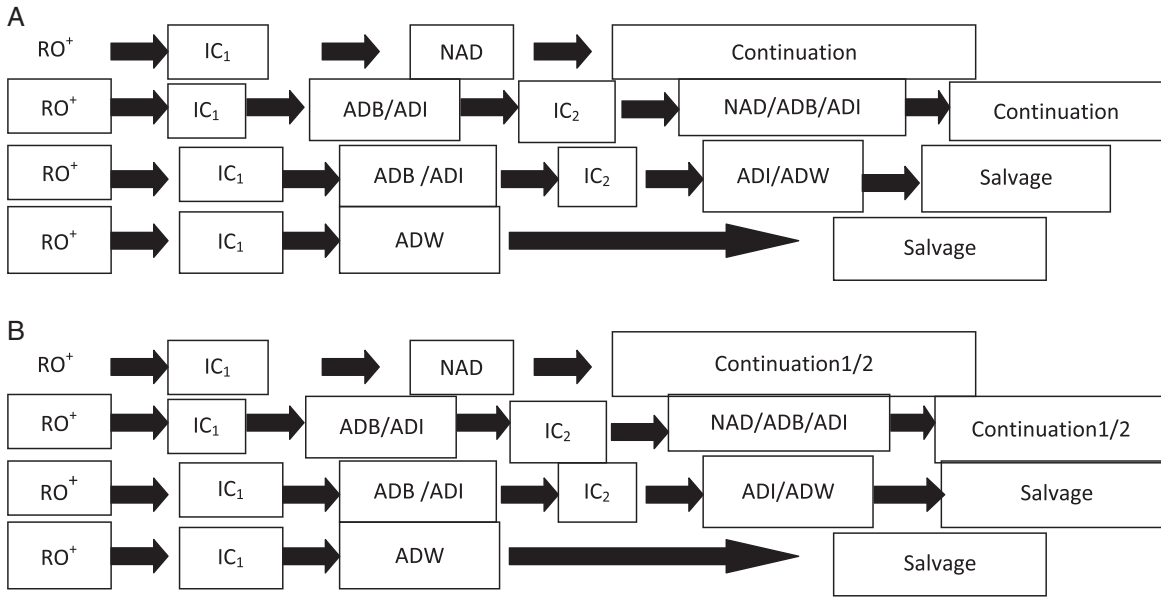

FIGURE 1. Roadmap of treatment before and after start 2012. A, Before 2012. IC1 induction I (week 1 to week 6): weekly intravenous vinblastine (VBL) 6 mg/m^2/d IV, oral prednisone (PRED) 40 mg/m^2/d for 4 weeks with tapering over 1 week, and intermediate-dose methotrexate (idMTX) 500 mg/m^2 every other week (week 1, week 3, week 5). IC2 Induction II (week 7 to week 12): weekly intravenous VBL 6 mg/m^2/d IV, weekly D1 to D3 oral PRED 40 mg/m^2/d, and idMTX 500 mg/m^2 every other week (week 7, week 9, week 11). Continuation VBL 6 mg/m^2 D1, oral PRED 40 mg/m^2 D1 to D5, daily 6 Mercapto-Purine (6MP) 50 mg/m^2, and weekly oral MTX 20 mg/m^2. B, After 2012. IC1 induction I (week 1 to week 6): weekly intravenous VBL 6 mg/m^2/d IV, oral PRED 40 mg/m^2/d for 4 weeks with tapering. IC2 induction II (week 7 to week 12): weekly intravenous VBL 6 mg/m^2/day IV, weekly D1 to D3 oral PRED 40 mg/m^2/d. Continuation 1 VBL 6 mg/m^2 D1, oral PRED 40 mg/m^2 D1 to D5, daily 6MP 50 mg/m^2. Continuation 2, 8 cycles of every 3 week vincristine 1.5 mg/m^2 D1, aracytine 100 mg/m^2/d D1 to D4, associated to PRED 40 mg/m^2 week 1/2, 20 mg/m^2/d week 3/4, 10 mg/m^2/d week 5/6, 5 mg/m^2/d week 7/8, followed by 6MP 50 mg/m^2/d/MTX 20 mg/m^2/d for 18 months. ADB indicates active disease better; ADI, active disease intermediate; ADW, active disease worse; idMTX, intermediate-dose methotrexate; NAD, no active disease; RO+, high-risk organ.

the costal margin. Both hepatomegaly and splenomegaly were confirmed by ultrasound. Lung involvement was confirmed with the presence of cysts or nodules on computed tomography radiologic examination.

First-line Treatment

The treatment consisted of an initial 6-week induction I, with subsequent 6-week Induction II if not achieving the targeted response, followed by 1-year continuation chemotherapy.[11] The roadmap of treatment before and after start 2012 is shown in Figures 1A and B.

Response to Treatment

Time of evaluation was dedicated to the end of first induction after week 6 or end of second induction after week 12. Evaluation was assessed as per the International LCH Study Group Criteria.[12] Better status: either nonactive disease (NAD) or active disease better (ADB). NAD is defined by no evidence of disease and resolution of all signs and symptoms. ADB is defined by regression of signs or symptoms without new lesions. Active disease intermediate is defined by persistence of signs or symptoms without new lesions or regression of existing lesions and appearance of new lesions at other sites, and active disease worse (ADW) is defined by progression of signs or symptoms and/or appearance of new lesions.

Treatment Failure

Disease progression (DP) or REA were considered to be a treatment failure. DP was recorded, if the patient showed active disease intermediate or ADW, at the end of reinduction II after week 12 or ADW at the end of induction I after week 6, in which case it was considered to start a second-line salvage. REA was recorded if the patient showed ADW after having achieved NAD or ADB at the end of induction and the start of continuation treatment.

Demography and stratification prognostic variables[8] were analyzed on their impact on overall survival (OS) and event-free survival (EFS), DP, and REA and included the following: (1) age category: 2 years and younger/ older than 2 years; (2) sex: male/female; (3) high-risk organ hemopoietic versus hepatic versus splenomegaly; (4) hemopoietic monocytopenia versus bicytopenia versus tricytopenia; (5) tricytopenia versus other cytopenias; (6) hepatomegaly versus hepatic dysfunction versus combined; (7) high-risk organs' combination tri, bi, mono (RO+): mono versus bi versus tri; (8) CNS risk bone site versus none; (9) lung affection versus none; (10) idMTX including regimen versus none; (11) Single versus double induction; (12) DP versus REA; (13) season of REA during autumn/winter (between September 21 and March 21) versus spring/summer; (14) number of REAs once versus more than once; (15) risk status at REA low-risk versus high-risk.

Data Collection and Statistical Analysis

All calculations were performed using IBM SPSS statistics 22.0. Kaplan-Meier analysis was used to estimate OS was calculated from date of diagnosis until date of last follow-up or date of death, and EFS was calculated from date of diagnosis until date of REA, DP, or death. Log-rank, chi

TABLE 1. Outcome According to IdMTX

UPN	Cytopenia	Hepatic Affection	Splenomegaly	Lung	W6	W12	Continuation	LFU
Not subjected to DP or REA								
2	N	HMG	N	No	ADB	ADB	VLB/Ste/MTX/ 6MP	Alive and well
3	Mono	HMG	N	No	ADB	ADB	VLB/Ste/MTX/ 6MP	Alive and well
8	Mono	HMG/hepatic dysfunction	Y	No	ADB	NAD	Vlb/Ste/MTX/ 6MP	Alive and well
11	N	HMG/hepatic dysfunction	Y	No	ADB	ADB	Vlb/Ste/MTX/ 6MP	Alive and well
13	N	HMG	N	No	ADI	ADB	Vlb/Ste/MTX/ 6MP	Alive and well
20	Mono	HMG	N	No	NAD	NAD	Vlb/Ste/MTX/ 6MP	Alive and well
21	N	HMG/hepatic dysfunction	N	No	ADB	ADB	Vlb/Ste/MTX/ 6MP	Alive and well

UPN	Cytopenia	Hepatic affection	Splenomegaly	Lung	W6	W12	Status	Cause of death
Subjected to (DP)								
6	Bi	Hepatic dysfunction	N	N	ADW	ADW	Died	ADW
9	Bi	HMG/hepatic dysfunction	Y	N	ADW Died	Died	Died	ADW
18	N	HMG	Y	N	ADW Died	Died	Died	ADW
22	N	HMG/hepatic dysfunction	N	N	ADB	ADW	NAD	Alive and well

UPN	Cytopenia	Hepatic affection	Splenomegaly	Lung	W6	W12	Continuation	Season	Reactivation risk	Timing reactivation	NREA	Organs	Status	Cause of death
Subjected to (REA)														
1	Bi	HMG/hepatic dysfunction	Y	No	ADI	ADB	VLB/Ste/MTX/ 6MP	Autumn/ winter	LR	After 1st year of end of ttt	1	PP, scalp	NAD	Alive and well
4	Bi	HMG	Y	No	ADI	ADB	VLB/Ste/MTX/ 6MP	Autumn/ winter	LR	During 1st year of end ttt	1	Orbit	NAD	Alive and well
5	Mono	Hepatic dysunction	N	Y	ADB	ADB	VLB/Ste/MTX/ 6MP	Autumn/ winter	HS	During continuation ttt	1	HMP	Died	ADW
7	Mono	HMG	N	N	ADB	ADB	VLB/Ste/MTX/ 6MP	Autumn/ winter	LR	After 1st year of end ttt	1	Bones, lung	NAD	Alive and well

TABLE 1. (*continued*)

UPN	Cytopenia	Hepatic Affection	Splenomegaly	Lung	W6	W12	Continuation	LFU					
10	N	HMG/hepatic dysfunction	N	Y	ADB	ADB	VLB/Ste/MTX/6MP	Autumn/winter	HR	During 1st year of end ttt	1	HMP, HSM	ADW	Alive in ADW
12	N	HMG/hepatic dysfunction	Y	Y	ADB	ADB	VLB/Ste/MTX/6MP	Autumn/winter	LR	During 1st year of end ttt	1	Bones	ADB	Alive and well
14	N	HMG/hepatic dysfunction	Y	N	ADB	ADB	VLB/Ste/MTX/6MP	Spring/summer	HR	During 1st year of end ttt	1	HSM, lung, LN, bones	NAD	Alive and well
15	Mono	HMG/hepatic dysfunction	Y	N	ADB	ADB	VLB/Ste/MTX/6MP	Autumn/winter	LR	Post 1st year of end ttt	1	Bones	NAD	Alive and well
17	Mono	HMG/hepatic dysfunction	Y	Y	ADB	ADB	VLB/Ste/MTX/6MP	Spring/summer	HR	During continuation ttt	1	HMP	Died	ADW

6MP indicates 6mercaptopurine; ADB, active disease better; ADW, active disease worse; DP, disease progession; HMG, hepatomegaly; HMP, hemopoietic; HR, high risk; HS, histiosarcoma; HSM, hepatosplenomegaly; LFU, last follow-up; LN, lymph node; LR, low risk; Mono, monocytopenia; MTX, methotrexate; N, no; NAD, no active disease; NREA, number of reactivation episodes; PP, posterior pituitary; REA, reactivation; Ste, steroids; Tri, tricytopenia; ttt, treatment; UPN, unique patient number; VCR, vincristine; VLB, vinbastine; Y, yes.

square, and Fisher exact tests were used to analyze the risk factors. The time of last follow-up was recorded for the survivors. *P*-values <0.05 were indicative of statistical significance and, if between 0.05 and 0.1, were indicative of a tendency to be statistically significant.

RESULTS

Clinical Characteristics

Fifty RO+ patients were involved in the study. Twenty-six were male individuals. The median age was 1.7 years (0.19 to 10.14). The high-risk organ involvement included hemopoietic system (n = 28, 56%), liver (hepatomegaly/hepatic dysfunction) (n = 48, 96%), splenomegaly (n = 30, 60%), and lung (n = 8, 16%). All patients received induction I with VBL/PRED, 20 of whom received idMTX in addition.

Thirty-eight patients received subsequent 6-week reinduction II course due to lack of the expected response.

Response and Failure of Induction

By the evaluation of the induction phase, death was reported from DP in 3 and 8 patients in the MTX group (n = 20), and non-idMTX (n = 30), respectively. The response after week 6 and week 12 according to id MTX including the regimen is shown in Tables 1 and 2 and Figure 2.

Outcome

The final outcome in the idMTX group and non-idMTX group is shown in Tables 1 and 2. The 3-year OS of the MTX and non-MTX groups are 75% confidence interval (CI), ± 19 and 63% CI, ± 20.6, respectively, $P = 0.537$ (Fig. 3), while the EFS was 36.9% CI, ± 21.8 and 13.2% CI, ± 13.5, respectively, $P = 0.005$ (Fig. 4), with a median follow-up period of 41.5 months. As regards the impact of treatment failure (DP or REA) versus none on survival, the 1-year OS was remarkably affected with the occurrence of DP versus REA versus none, wherein it was 47.1% CI, ± 20,7; 92.9% CI, ± 13.5; and 94.7% CI, ± 9.996, respectively, $P = 0.001$.

Prognostic Factors

The factors that were associated with both poor OS and EFS and were statistically significant are highlighted in Table 3. The factors associated with DP upon induction were tricytopenia ($P = 0.001$) and hepatic dysfunction ($P = 0.027$). There was a tendency for statistical significance between DP and the non-idMTX regimen, $P = 0.075$. The factors associated with REA were male sex, ($P = 0.014$), season (autumn/winter) ($P = 0.01$), lung disease ($P = 0.03$), and idMTX regimen ($P = 0.029$).

DISCUSSION

Despite the benign course of LCH in general, its high-risk form, RO+, fortunately less common, still carries a bad prognosis with 2 drug regimens, VBL and PRED. For this reason, the first-line in RO+ group, has always been the subject of trials and debate. In our single-center experience, we tried to evaluate the outcome of 50 RO+ LCH patients, over a relatively prolonged period of time, reaching > 8 years. They were subjected to 2 eras of treatment: the first one, before start of 2012, having idMTX during induction, and, the second era, afterwards, without idMTX. This was omitted according to the preliminary results of the Histiocytosis Society doubting its beneficial effect.[8] This study, being a retrospective one, although it carries risk of

TABLE 2. Outcome According to Non-idMTX

	Cytopenia	Hepatic Affection	Splenomegaly	Lung	W6	W12	Continuation	LFU
Not subjected to DP or REA								
23	Bi	HMG/hepatic dysfunction	Y	N	ADB	ADB	VLB/Ste/6MP	Alive and well
24	Mono	Hepatic dysfunction	N	N	ADB	ADB	VLB/Ste/6MP	Alive and well
27	N	HMG	N	N	ADB	NAD	VLB/Ste/6MP	Alive and well
30	N	HMG	Y	N	ADB	ADB	VLB/Ste/6MP	Alive and well
36	N	HMG	N	Y	ADB	NAD	VCR/ARAC/ Ste/6MP/MTX	Alive and well
38	N	HMG	Y	N	ADB	ADB	VCR/ARAC/ Ste/6MP/MTX	Alive and well
39	Mono	HMG/hepatic dysfunction	N	N	ADB	ADB	VCR/ARAC/ Ste/6MP/MTX	Alive and well
44	N	HMG/hepatic dysfunction	N	N	ADB	NAD	VLB/Ste	Alive and well
46	N	N	N	N	ADB	ADB	VCR/ARAC/ Ste/6MP/MTX	Alive and well
47	N	HMG	Y	N	ADB	ADB	VCR/ARAC/ Ste/6MP/MTX	Alive and well
48	Bi	HMG/hepatic dysfunction	Y	N	ADB	ADB	VCR/ARAC/ Ste/6MP/MTX	Alive and well
50	N	HMG/hepatic dysfunction	Y	N	ADB	ADB	VCR/ARAC/ Ste/6MP/MTX	Alive and well
UPN Subjected to DP	Cytopenia	Hepatic affection	Splenomegaly	Lung	W6	W12	Status	Cause of death
25	Tri	HMG/hepatic dysfunction	Y	N	ADI	ADW	Died	ADW
28	Tri	HMG/hepatic dysfunction	Y	N	ADB	ADW	Died	ADW
29	Tri	Hepatic dysfunction	N	N	ADB	ADW	Died	ADW
31	Tri	HMG/hepatic dysfunction	Y	Y	ADB	ADW and died	Died	ADW
32	N	HMG/hepatic dysfunction	Y	N	ADW	On salvage	Died	ADW
34	Mono	HMG/hepatic dysfunction	Y	N	ADB	ADW and died	Died	ADW
35	Tri	HMG/hepatic dysfunction	Y	N	ADB	ADW	NAD	Alive and well

TABLE 2. (*continued*)

	Cytopenia	Hepatic Affection	Splenomegaly	Lung	W6	W12	Continuation	LFU
37	Mono	HMG/hepatic dysfunction	N	Y	ADW	On salvage	NAD	Alive and well
40	Tri	HMG/hepatic dysfunction	Y	N	ADB	ADW	NAD	Alive and well
41	Mono	HMG/hepatic dysfunction	Y	N	ADB	ADI	ADW	Alive in ADW
42	N	HMG/hepatic dysfunction	N	N	ADW	On salvage	ADB	Alive and well
45	Tri	HMG/hepatic dysfunction	Y	N	ADW	ADW and died	Died	ADW
49	No	HMG/hepatic dysfunction	Y	N	ADW	On salvage	Died	ADW

UPN Subjected to REA	Cytopenia	Hepatic affection	Splenomegaly	Lung	Continuation	W6	W12	Season REA	REA risk	Timing REA	NREA	Organs	Status	Cause of death
16	N	HMG	Y	N	VLB/Ste/6MP	ADB	ADB	Spring/ summer	HR	During continuation ttt	3	HMP, spleen, bone, skin	ADB	Alive and well
19	Bi	HMG	N	N	VLB/Ste/6MP	ADI	NAD	Autumn/ winter	LR	During continuation ttt	1	Bone	NAD	Alive and well
26	Mono	HMG/hepatic dysfunction	Y	N	VLB/Ste/6MP	ADB	ADB	Autumn/ winter	HR	During 1st year of end end ttt	1	HMP, spleen	Died	ADW
33	N	N	Y	N	VLB/Ste/6MP	NAD	NAD	Autumn/ winter	HR	During continuation ttt	1	HMP, HSM	NAD	Alive and well
43	Bi	HMG/hepatic dysfunction	Y	Y	VCR/ARAC/ Ste/6MP/MTX	ADB	ADB	Spring/ summer	HR	During continuation ttt	1	HMP, HSM, lungs	ADB	Alive and well

6MP indicates 6mercaptopurine; ADB, active disease better; ADW, active disease worse; ARAC, aracytine; Bi, bicytopenia; DP, disease progession; HMG, hepatomegaly; HMP, hemopoietic; HR, high risk; HS, histiosarcoma; HSM, hepatosplenomegaly; LFU, last follow-up; LN, lymph node; LR, low risk; Mono, monocytopenia; MTX, methotrexate; N, no; NAD, no active disease; NREA, number of reactivation episodes; REA, reactivation; Ste, steroids; Tri, tricytopenia; ttt, treatment; UPN, unique patient number; VCR, vincristine; VLB, vinbastine; Y, yes.

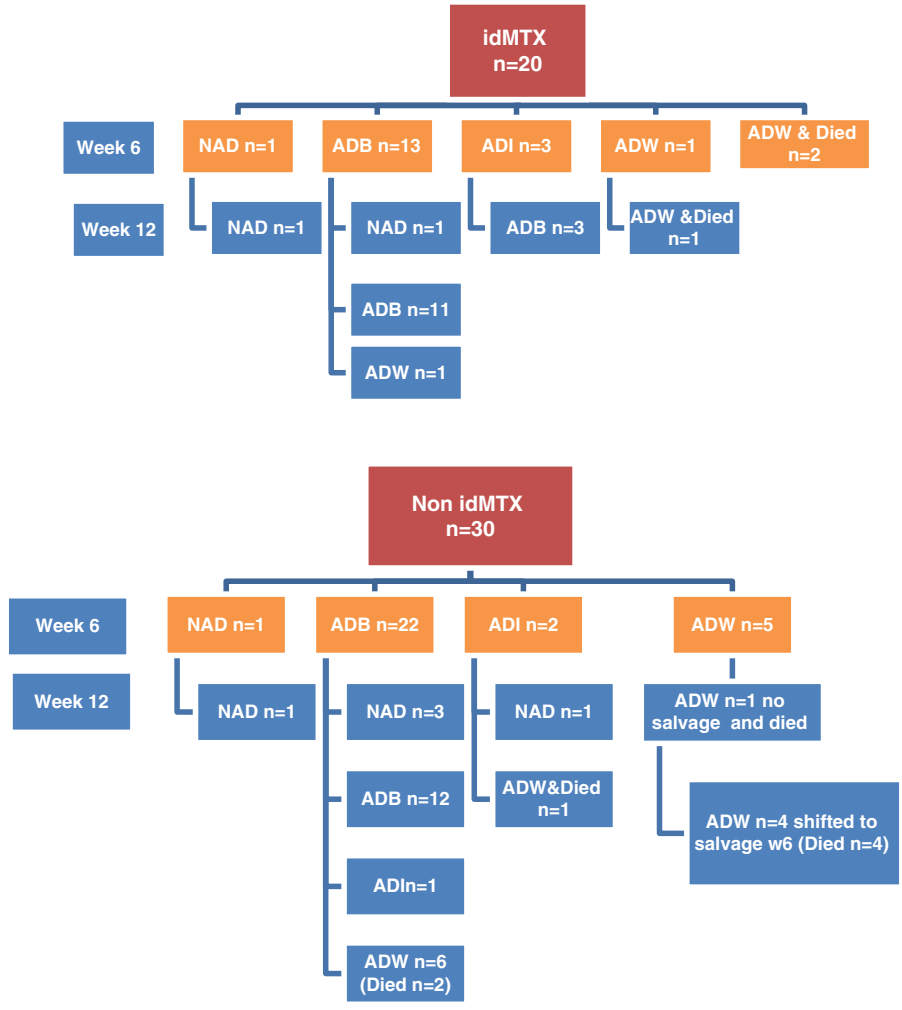

FIGURE 2. Response to first-line treatment according to idMTX including regimen. ADB indicates active disease better; ADI, active disease intermediate; ADW, active disease worse; idMTX, intermediate-dose methotrexate; NAD, no active disease. full color online

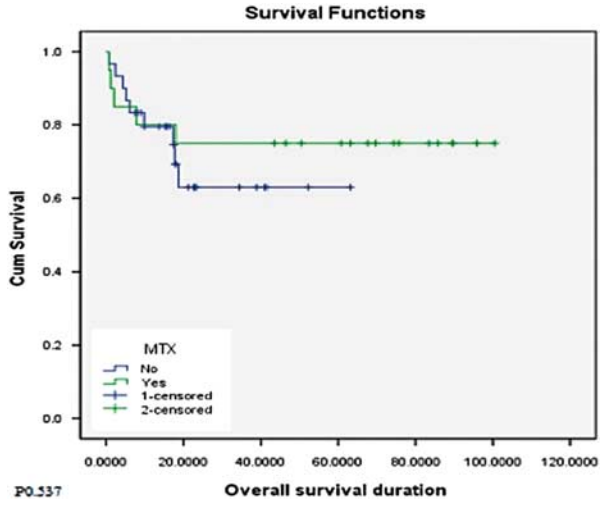

FIGURE 3. The 3-year overall survival and methotrexate (MTX). full color online

biases, is still one of the few single-center experiences that provide interesting information on the outcome of a subgroup of a rare orphan disease treated through 2 different strategies.

In a 22 years' experience of 154 patients at a single center where of 29 patients receiving induction regimen including PRED, VBL, MTX, and cyclophosphamide, only 2 patients showed DP, and the 5-year progression-free survival was 52%.[13] However, in another randomized controlled trial of the Histiocytosis Society, Gadner et al[8] showed in the LCH III protocol that, the addition of idMTX did not increase disease response, as the responders in the MTX arm were 72% versus 70% in the non-MTX arm ($P = 0.81$).

In our study, contrarily to these results,[8] we found a useful role of idMTX, as regards a statistically significant better 3-year EFS, and better impact of idMTX on OS. However, this proved statistically nonsignificant; it still exists as a deviation toward significance ($0.05 < P < 0.1$). This could be explained by a low mortality in both groups in a small sample size.

These results are less than the overall 5-year survival probability of RO+ patients in LCH-III, 84%.[8] Those results were substantially higher than in the corresponding

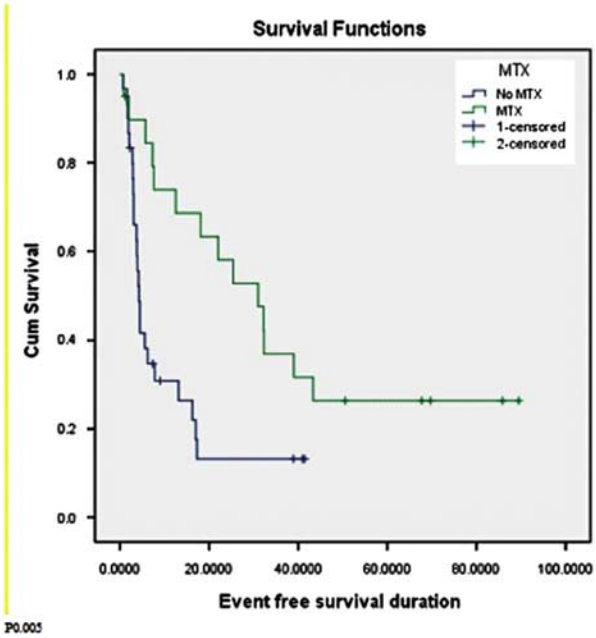

FIGURE 4. The 3-year event-free survival and methotrexate (MTX). full color online

(historical) RO+ patients in the predecessor trials LCH-I (62%)[14] and LCH-II (69%).[4] In the Korean experience, over a period of 22 years, the OS and EFS of patients with high-risk organ involvement was 89% and 52%, respectively.[13] In the Japanese study of pediatric multifocal LCH, the OS and EFS at 5 years was 94% and 39%, respectively, and there was no difference between low-risk and high-risk organ subgroups.[15]

After week 12, the definitive timing of evaluation of induction, we found that the induction group including idMTX showed more "Better Status" than that in the non-idMTX group.

In our series, DP at the end of induction was more in the non-MTX group in relation to the MTX group, with a tendency for statistical significance ($0.05 < P < 0.1$). This might be explained by the 2 unequal small-sized population groups.

Interestingly, disease REA was frequent, as it occurred in nearly half of the idMTX group, while it occurred in one fifth of the non-idMTX group. The association between MTX and REA proved to be statistically significant.

These findings need more investigations in further randomized controlled studies. The outcome of REA is acceptable in relation to the dismal one in DP upon induction. In the study carried out by the HS LCHIII, RO+ patients' REA rate of 27% was similar in both groups.[8] As regards treatment failure outcome, in our series, DP at the end of induction was responsible for lesser OS in relation to REA and no treatment failure with statistically significant results.

The different factors affecting OS or EFS in our series were cytopenias, wherein trihemopoietic cytopenia was associated with lesser survival. This was shown by the study by Galluzo et al[16] wherein patients with trilineage or bilineage cytopenias were significantly associated with death. This might be due to the association with hemophagocytosis.

It was the same with liver involvement, as hepatic dysfunction in itself was associated with significantly worse survival in relation to isolated hepatomegaly. This could be

TABLE 3. Prognostic Factors With OS and EFS

Factors With OS	Incidence	OS	*P*
Cytopenia			
Tricytopenia	6	50% (±39.984)	0.019
Others	44	84% (±10.78)	
Liver affection	48 (96%)		
Hepatomegaly	14	92.9% (±13.524)	0.027
Hepatic dysfunction	4	25% (±42.532)	
Bi	30	80% (±14.308)	
High-risk combination			0.024
Mono	14 (28%)	100%	
Bi	19 (38%)	73.7% (±19.796)	
Tri	17 (34%)	70.6% (±21.756)	
No. inductions			
Single induction	12	58.3% (±27.832)	0.026
Double induction	38	86.5% (±10.976)	
Failure of treatment			
Disease progression post induction	17	17.6 (±34.496)	0.001
Reactivation	14	66.3 (±22.54)	
Factors with EFS	Incidence	EFS	
Cytopenia			
None	22	42.5% (±22.148)	<0.001
Monocytopenia	13	44.9% (±27.636)	
Bicytopenia	8	28.6% (±33.516)	
Tricytopenia	7	14.3% (±25.872)	
Hepatomegaly	14	61.9% (±26.656)	0.017
Hepatic dysfunction	4	25% (±42.532) 3 events of 4 patients	
Combined	30	22.7% (±15.876)	
High-risk organs' combination			
Bi	19	50.5% (±23.324)	0.047
Tri	30	25.6% (±16.856)	
CNS risk bone site	27	17.9% (±16.268)	0.030
No CNS risk site	23	54.7% (±20.776)	
Single induction	12	18.5% (±23.128)	0.017
Double induction	38	39.1% (±16.66)	

CNS indicates central nervous system; EFS, event-free survival; OS, overall survival.

partially explained by an overestimation of hepatic affection by organomegaly on the basis of subjective clinical physician opinion. Otherwise, simple hepatomegaly is a common and nonspecific clinical finding. However, others reported very variable incidence of hepatic affection of between 10% and 45%.[6,17–19]

The number of RO+ was inversely proportional with survival as triorgan affection combination: hemopoietic system, hepatomegaly, and splenomegaly were associated with a statistically significant lesser survival outcome. This seems to be comprehensive with hemophagocytic component or the inclusion of the known previously called Litterer Siwe disease.[20,21]

Double induction showed to significantly improve both OS and EFS. This is contradictory to what has been claimed by others.[4] This contradiction could be explained by the subjective assessment according to International LCH Study Group Criteria.[12] False-positive ADB after induction I rather than no active disease could have subjected patients to unnecessary reinduction II. This calls for a more objective scoring system.

More factors related to REA included male gender, seasonal variation more in autumn/winter, and association with

lung involvement, with statistically significant association. Seasonal autumn-winter association with REA might carry a viral agent for REA.[22] These observations need to be elucidated in further larger multicenter future studies. In our study, CNS risk site bony affection was shown to lower EFS. This was confirmed previously with monostotic CNS risk site lesions to be associated with increased morbidity.[23]

CONCLUSIONS

IdMTX is associated with better EFS. DP on induction remains of dismal prognosis in relation to disease REA afterwards. Risk stratification should highlight the role of trihemopoietic cytopenias, hepatic dysfunction, tri RO+, CNS risk site, and lung association.

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