Management of functional, hepatic damage after chemotherapy with Liverubin® (pharma-standard silymarin)

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Aim. **Mild, temporary hepatic failure (MTHF) after chemotherapy is a common clinical problem; in case of repeated episodes MTHF may cause chronic impairment.**
Methods. **This registry has evaluated post-chemotherapy (PC)-MTHF in subjects using Liverubin® (standardized water soluble silymarin) for 8 weeks (3 tablets/day). *PC*-MTHF was evaluated in a registry study. Hepatitis markers were negative at inclusion and at end-registry. There were results concerning 18 Liverubin-supplemented patients and 19 controls completed in the 8-week period. The distribution of the most common symptoms and signs with ultrasound scans were comparable. Symptoms were mostly minimal or subclinical. Symptoms observed at inclusion were completely disappeared or were greatly attenuated after 8 weeks. The improvement produced by Liverubin® resulted in inducing a better and faster disappearance of symptoms.**
Results. **The results of the blood tests (at inclusion and at 8 weeks showed significant increase in albumin, significantly (P<0.05) faster with the final values higher in the supplement group. Total bilirubin was reduced within the supplement group better than in controls (P<0.05). Direct bilirubin values improved more in the supplement group (P<0.05). The decrease in ALT-SGPT and AST-ASAT was more evident with the supplement group (P<0.05). Improvement in controls was more limited. Alkaline phosphatase was lower (than in controls) with Liverubin® at 8 weeks (p<0.05). GGT also decreased more and faster with the supplement. The ESR (erythrocytes sedimentation rate) was decreased in both groups, more in the Liverubin® group (P<0.05). There was a more limited decrease in controls with persisting higher values at 8 weeks. The white cell count was also better at 3 months (with a larger decrease with the supplement; P<0.05). Plasma free radicals (PFR) were elevated in both groups at inclusion. A more significant decrease in the PFR supplement group was observed at 8 weeks. Persistant elevation in values was seen in controls (P<0.05). Platelets values improved better with Liverubin® (P<0.05). Safety and tolerability were optimal (no side effect was registered).**
Conclusion. **In conclusion, results from this pilot registry indicate a significant activity of Liverubin® associated with a very good safety profile, in patients with post-chemotherapy hepatic failure. The recovery of hepatic function is faster and more effective with Liverubin® in comparison with the best "standard" management.**

KEY WORDS: Chemotherapy - Liver failure - Hepatitis - Silymarin - Liverubin - Hepatic enzymes - Liver - Jaundice - Bilirubin.

Hepatic insufficiency may be caused by infective or non-infective causes (food, drugs, alcohol, a combination of elements but also by chemotherapy).

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After chemotherapy, mild temporary hepatic failure (MTHF) may be asymptomatic.[1-8] This common problem, when caused by chemotherapy, could be associated with significant clinical symptoms in many oncological patients. Chemotherapy may cause both functional alterations and lead to cell necrosis and severe hepatic organic changes. Chemotherapy-induced liver disease may complicate the life and management of many patients with tumors reducing their quality of life.

The rate of hepatic complication following the use of chemotherapic medications is probably high; most episodes may be subclinical and undiagnosed or included in the general clinical picture associated with the primary oncological problem.[1-8]

Hepatotoxicity is also associated or aggravated by several anti-inflammatory compounds that may be used to contrast the symptomatic effects of chemotherapy or to control pain due to the tumors.[4-7]

Liver enzymes may be altered in most patients after chemotherapy and are generally diagnostic parameters for MTHF.

The management of MTHF [3, 7] is based on avoiding – when and if possible the toxic or damaging agents and situations increasing functional damage. Viral hepatitis, should be always excluded in any patients with MTHF.

At the moment, there is no defined standard of treatment.[3, 7] Avoiding further damage and metabolic stress is a key element in management. Hydration, diet, observation (repeating blood tests, particularly the enzymes associated with MTHF) define the supportive management.[7] Some pharmacological agents have been used and are still used (including steroids). There is, however, no therapeutic standard. N-acetylcysteine may be effective in some cases of undefined, acute liver failure.[2-12]

A recent study [2] has indicated a protective effect of a specific oak wood extract (Robuvit) on liver injury.

Liverubin® and silymarin have also been used in several clinical studies.[3, 4, 16, 17] Liverubin® (produced by Alchem, India) is a standardardized formulation based on the synthesis from Milk Thistle seeds used in the management of liver damage. Sylimarin has been extensively studied and used to manage hepatic dysfunction.[2, 3, 7]

The aim of this pilot registry was to evaluate the evolution of post-chemotherapy MTHF in oncological subjects using Liverubin® for 8 weeks after chemotherapy.

Materials and methods

Inclusion criteria

Patients with PC-MTHF were studied in a registry study. In all registered subjects viral hepatitis markers were negative. Other possible causes of MTHF (including alcohol and drugs) had been evaluated (Table I), documented or excluded. The registry patients were characterized by PC-MTHF associated to decreased albumin levels, increased total bilirubin, altered hepatic function enzymes and an increase in oxidative stress.

Management of MTHF

For initial liver failure the best management option is to avoid further negative effects of specific toxic agents. Patients must have an adequate diet, rest and sleep, good hydration also improved lifestyle (avoiding alcohol and any potential, damaging agents). This open-label, registry included patients with a clinical and laboratory diagnosis of acute, moderate hepatic insufficiency based on enzymes and blood tests and on an evaluation of the liver with high-resolution ultrasound that excluded anatomic and organic lesions, particularly liver metastases.

Exclusion criteria

Recent (less than 6 months) surgery, Body Mass Index (BMI) <27 and obesity were considered exclusion as well as unstable, severe or rapidly progressing disease, renal disease, history of hepatitis, HIV, metabolic disorders requiring treatment and anemia. Congenital liver abnormalities, unstable mood, attention disorders, addictions, medical history requiring other treatments (including barbiturates or antiepilep-

tic medications) excluded the patients from the registry.

Signs and symptoms

Signs and symptoms were observed and were considered for inclusion in this registry (at least 3 symptoms were present in the weeks before inclusion) in associations with laboratory alterations. Signs and symptoms variations were considered a secondary target (not all patients clearly show symptoms).

Tiredness, fatigue, change in urine color, malaise, nausea, vomiting, upper right quadrant tenderness or pain were variably present in the registry subjects and not necessarily associated to the liver dysfunction. Ultrasound-documented mild, liver enlargement and mild splenomegaly were also present in all included subjects (Table I).

Liverubin® (Alchem) was used at the dosage of 3 tablets (each equivalent to 140 mg) daily.

Plasma free radicals

Oxidative stress in plasma was measured with a drop of blood in seconds, as validated in several studies.[18] This method measures reactive oxygen species in peripheral blood (measurements were expressed in Carr Units).

All blood tests evaluated at inclusion and repeated at 3 months.

Supplement studies

Supplement, registry studies [19] define the field of activity of supplements and possibly preventive, preferably non-clinical, applications. The best fields of application for supplements are preclinical, borderline applications or the supplementary management of risk conditions. Supplements, unless there are specific claims, are not generally used for treatment of signs and symptoms or clinical conditions. The aim of supplement studies is to produce supplementary data to be compared to "background" historical data (i.e., based on the best available management for comparable subjects) or to other management plans. In this study the supplement was used according to the following rules:

1. The use of the supplement was suggested to the evaluation subjects; the supplement use was not prescribed but suggested as an option, possibly capable of improving the management of the risk condition;

2. The supplement was only used on top of what was considered the "standard" or best-management/care available, for that condition, according to international guidelines;

3. The use of the supplement should not have interfered with any other treatment, management or preventive measure;

4. Time: the period of follow-up was considered variable, according to the needs and availability of the patients or registry subjects. The observation period is therefore variable, not prefixed. Ideally, the supplement administration should be used as long as needed to see results or changes;

5. The type of evaluation for these studies is always a registry. The evaluation of the compliance concerning the use of the supplement is a significant value indicating

TABLE I.—*Types of tumors treated with chemotherapy inducing liver failure.*

	Liverubin®+SM	Controls
Number	18	19
LOST	6	9
– Gastric	3	3
– Colon	9	8
– Colon-rectal	6	8

Characteristics: no hepatic, lung or brain metastases. First cycle. No other clinical or metabolic disease. No other drugs. No hepatitis. Hep markers were negative. Before inclusion into chemotherapy cycle.

how many subjects are actually willing to use the product. In these supplement studies there is no defined group allocation, no randomization organized by the investigators. Subjects decide, on the basis of the initial briefing, the management group they want to join including the control (non-supplement) group. No placebo is used.

Open label

Patients are always informed about the supplement or any treatment and management measure. A possible placebo effect is carefully explained and considered.

Data and results are analyzed only after the observation period, ideally, when sufficient evidence is collected or when fund limitations would eventually stop the collection of the observations. The time needed to detect differences among group is also considered an evaluation target. In this type of studies, control groups, if present, are not necessarily parallel.

This study – following a previous model study on Liverubin®[3] was a pilot, independent, registry study; the evaluation product was not prescribed but recommended. Commercial sponsorship from the producers of the tested supplement was not available.

Safety and tolerability

Safety and tolerability were assessed by clinical evaluation and laboratory measurements. Possible adverse experiences were monitored. Clinical adverse experiences were evaluated for intensity, considering duration, seriousness, outcome, and relationship to the study drug.[3, 4]

Chemotherapy had been completed – for all registry patients – at least 2 weeks before and there was no plan for chemotherapy for the next 3 months.

Statistical analysis

Sample sizes were determined (at least 15 subjects in each group) on the basis of a previous comparable study. Clinical and blood tests data were considered as non-parametric. An analysis of covariance (ANCOVA) model was used considering supplemented subjects vs controls – both for symptoms and blood tests and their variability using standard management with the corresponding 90% confidence intervals (CI).

Results

Table I indicates the distribution of patients within the two resulting groups. In the final registry there were reliable results concerning 18 Liverubin® patients and 19 comparable controls completing the full period (Table II). There were 6 dropouts in the supplement group and 9 among controls. All drops were due to minor complications relative to the oncological management; none was caused by the supplementary management with Liverubin®. The average follow-up period was between 62;2.2 days in the supplement group and 63.3;4.1 days in controls.

Signs and symptoms

Table II shows the distribution of the most common symptoms and signs with ultrasound scans. The two groups (Liverubin® + best management and best management only) were comparable at inclusion. Symptoms were mostly minimal or subclinical. Most symptoms observed at inclusion completely disappeared or were greatly attenuated after 8 weeks. The improvement produced by Liverubin® induced a better and faster disappearance of symptoms.

TABLE II.—*Details of the two management registry groups (A). Drop-outs were due to missed controls.*

Number	Group		Management
18	LIVERUBIN® (LR)	(age range 44-66; 12 males)	BEST MANAGEMENT + LR
19	CONTROLS	(age range 41-67; 10 males)	BEST MANAGEMENT ONLY

P<0.05 in comparison with controls.

TABLE III.—*Signs/symptoms at inclusion and 8 weeks later. The number of patients with the symptom out of the total group is indicated.*

	Liverubin®+SM		Controls	
	Inclusion	2 months	Inclusion	2 months
Fatigue	18/18	10/18*	19/19	11/19
Tiredness	18/18	7/18*	19/19	12/19
Change in urine color	18/18	4/18*	19/19	7/19
Malaise	18/18	6/18*	19/19	11/19
Nausea-vomiting	16/18	2/18*	19/19	4/19
Abdominal upper right quadrant				
– Tenderness/pain	11/18	6/18*	12/19	9/19
– Ultrasound-documented liver enlargement	18/18	10/18*	19/19	12/19

Table III shows the results of the blood tests (inclusion and at end-registry). The increase in albumin was significantly (P<0.05 at 3 months) faster and the final values were significantly higher with Liverubin®.

Total bilirubin was reduced with the supplement better than in controls (P<0.05). Direct bilirubin values improved more in the supplement (P<0.05). The decrease in ALT-SGPT and AST-ASAT was more evident with the supplement (P<0.05). Improvement in controls was more limited.

Alkaline phosphatase was significantly lower (than in controls) with Liverubin® at 8 weeks (P<0.05). GGT also decreased more and faster with the supplement. The ESR (erythrocite sedimentation rate) was decreased in both groups, more in the Liverubin® group (P<0.05). There was a more limited decrease in controls with persisting higher values at 8 weeks. The white cell count was also better at 3 months (with a larger decrease with the supplement; P<0.05).

Oxidative stress

Plasma free radicals (PFR) were elevated in both groups at inclusion. A more significant decrease in the supplement group was observed at 8 weeks. Persisting elevation in values was seen in controls (P<0.05). This difference was particularly significant.

Platelets values also significantly improved in the Liverubin® group (P<0.05) better than in controls.

Other blood tests (including hematocrit, renal function tests) were within the normal range at inclusion and at 8 weeks in both groups. Hepatitis markers were also negative when repeated at end-registry in all subjects. Also ultrasound scans did not reveal any liver metastases at 8 weeks.

Compliance: 95% of the Liverubin® tablets were correctly and regularly used. Safety was optimal and no side effects were registered. Tolerability was optimal; no patient had to stop treatment.

Discussion

Hepatic function alterations after chemotherapy are very common and due to multiple and very challenging causes. Often the subclinical picture is confusing and difficult to diagnose early in most patients.

Treatment with silymarin extracts in this condition has long traditional roots. Previous studies have indicated the safety and efficacy of Liverubin®.[2, 4]

Repeated hepatic damage and the associated increase in oxidative stress may cause severe functional and organic liver damage that later may become permanent.

MTHF is generally diagnosed by the observation of altered enzymes while signs and symptoms may still be vague.

GGT may be elevated even in minor, subclinical hepatic conditions associated to chemotherapy. This test may identify the cause of an isolated elevation in ALP (as GGT is raised in alcohol toxicity). Improvements and the normalization in enzymes

TABLE IV.—*Results at 1 and 2 months.*

	Range	Units	Groups	Inclusion	2 months
1. Albumin	3.5-5.3	g/dl	LR	3.04;1.2	4.4;1 *#
			Controls	3.22;1	3.73;0.9*
2. TOTAL BIL	0.2-1.2	mg/dl	LR	3.2;1.1	1.23;0.5*#
			Controls	3.32;0.9	1.84;0.8*
3. DIRECT BIL	0.1-0.4		LR	0.1;0.03	0.24;0.04*#
			Controls	0.11;0.06	0.1;0.06*
4. ALT-SGPT	7-56	IU/L	LR	239.3;26	87.2;14*#
			Controls	253.3;24	102.6;12*
5. AST-ASAT	5-47	IU/L	LR	175;33	68.4;17**#
			Controls	169.3;27	104.3;22*
6. ALK PHOSPHATE (ALP)	30-120	IU/L	LR	226.4;34	157;22*
			Controls	234.5;29	173.4;22*#
7. GGT	10-42	IU/L	LR	149.3;31	76.3;22*#
			Controls	144.5;35	97.4;23*
7. ESR	0-23	mm/h	LR	55.9;9	37.6;8*#
			Controls	59.4;12	44.3;9*
8. White Cell Count			LR	7455;1033	5336; 985*#
			Controls	6739;1054	6666; 1027*
9. PLATELETS			LR	198 446*	207 358 *#
			Controls	184 367	176 553*
10. Ox stress	<310	Carr units	LR	437.4;34	365.5;24*#
			Controls	441.2;31	396.3;22*

. *P<0.05 in comparison with previous value.
#P<0.05: difference between groups at 8 weeks.

are considered an indication of clinical improvement. The enzymatic tests are effectively used to monitor MTHF after drug or alcohol toxicity. In this registry GGT (elevated at inclusion) was more significantly reduced with Liverubin® administration in comparison with the control management.

Silymarin extracts – and particularly Liverubin® - have a protective effects on liver and act selectively on hepatic injury in most cases of functional hepatic failure.

Liverubin® is highly standardized and is particularly soluble in water; this improves its bioavailability (2-3 times higher in comparison with other silymarin preparations).[3, 4]

The effects of silymarin and (specifically Liverubin®) in PC-MTHF are most probably the result of a significant, acute, hepatotropic anti-inflammatory action at hepatocytic level associated to a significant anti-oxidant action.

Pharma-standard supplements evaluated in open registries, as a comparative base the best present management *versus* the best management plus the supplement, are an important possible solution to evaluate new, possible management solutions to common clinical problems.

Conclusion

In conclusion, the results of this pilot registry indicate and confirm a significant activity of Liverubin® associated with a very good safety profile, in hepatic failure.

Recovery of hepatic function is faster and more effective with Liverubin®.

The hepatoprotective activities of Liverubin® appear to be mediated by their strong antioxidant effects in conditions of increased oxidative and cellular stress.

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