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Intravenous UDCA Administration during Cancer Chemotherapy, Liver Failure and Oral Route not Available

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Abstract

➢ ***Introduction:***

The chemotherapy of solid primary tumors with or without liver metastasis, very often impairs liver function causing high level of transaminase, GGT, bilirubin, alkaline phosphatase, and low albumin level due to intrinsic toxicity. The concept to add UDCA during or after chemotherapy cycles whenever liver toxicity risk is reasonably high, or impending, or already stabilized with variable digestive symptoms and low life quality, is nowadays very appealing.

Unfortunately, many patients cannot tolerate the oral prescription of full or reduced UDCA dosages because of compromised digestive conditions, for gut obstruction. Sub obstruction (from esophagus, stomach, duodenum down to colon) malabsorption, side effects, etc, being many people under total parenteral nutrition (TPN) even unable to swallow fluids.

➢ ***Materials and Methods:***

In a cohort of 100 patients, both sex often with coexisting synchronous or metachronous liver metastasis and liver enzymes/bilirubin impairment, and very often with GI tract troubles due to oral medications, or even problem with food absorption, and gut transit impairment; we evaluated the possible subjective/objective benefits of intravenous bile salts therapy, in an plain open simple trial, whose primary end point was:

- **The life quality improvement (icterus asthenia, fatigue, dyspepsia, mesogastric and liver pain, bloating, itching),**
- **Control of the toxic chemotherapy symptoms and lab exams amelioration**

➢ ***Results:***

The life quality of the treated patients was definitely improved by parenteral UDCA perfusion, particularly as to the digestive symptoms and liver enzymes imbalance, the tolerance was excellent, and the benefits followed up over one month.

➢ ***Conclusions:***

Parenteral UDCA administration is very helpful during the current chemotherapy regimens of cancer patients to relieve drug toxicity and help liver detox enzymes.

We recommend specifically intravenous treatment when the liver parenchyma is affected by primary or metastatic malignant cancers and whenever gastrointestinal impairment such as obstruction or subobstruction any level, IBD, prolonged fasting and parenteral nutrition inhibit the physiologic enterohepatic bile acids cycle.

I. INTRODUCTION

Ursodeoxycholic acid (UDCA) is a secondary bile acid transformed by intestinal bacteria from (cheno)deoxycholic acid, with several functions in the control of enteric flora, ileocolic barrier integrity, lipid absorption and metabolism. Internationally acknowledged and registered as a drug, it has been licensed and authorized for the litholytic treatment of cholesterol gallstones, primary biliary cholangitis, and other hepatobiliary disorders.

UDCA role has recently been re-evaluated as preventive agent against damages induced by cancer chemotherapy drugs, based on its anti-inflammatory, antioxidant and cytoprotective activities but also as complementary adjunct to some chemotherapy protocols such as sorafenib for liver cancer, due to it's antiapoptotic (normal epithelial cells), apoptotic/autophagic properties(of cancer cells) **[1].**

It also inhibits cancer stem cells migration and improves chemotherapy induced dysbiosis; specific activity has been registered against gastric and colon cancers: in flutamide (anti prostatic cancer chemo-agent) induced hepatitis. It has been proven very effective in reducing jaundice and restoring liver function after drug with drawl **[2]**.

ISSN No:-2456-2165

In another study by Ikegami and coworkers **[3]**, **UDCA increased the apoptosis due to DNA topoisomerase inhibitor through a mechanism of caspase 9 and caspase 3 activation**: this is another potential clinical support to enhance the effects of the chemo.

II. MATERIALS AND METHODS

100 patients volunteers (41 males and 59 females), coming from the emergency Dept., aged between 30 and 80 years, appealed to our "Second Opinion Medical Consulting Network, Medical Centre (Modena, Italy), because of coexisting synchronous or metachronous liver metastasis and liver enzymes/bilirubin impairment, and very often with GI tract troubles due to oral medications, or even problem with food absorption, and gut transit impairment.

The Second Opinion Medical Network is a consultation referral web and Medical Office System recruiting suddenly a wide panel of real-time available specialists, to whom any patient affected by any disease or syndrome and not adequately satisfied by the diagnosis or therapy can apply for an individual clinical audit **[4]**. Due to the doctor-patient communication gap, most of the patients usually wander around the medical websites looking for proper answers to their health problems. However, their search often becomes compulsive and obsessive and often ambiguous and frustrating **[5]**. Palmieri et al. **[6]** describe this borderline or even pathological behavior as the "Web Babel Syndrome" – a psychological imbalance affecting young and elderly patients, especially those with multiple synchronous diseases who receive from their caregivers heterogeneous and misleading information or advices, including confused, contradictory statements and prescriptions **[7]**. To deal with this problem, the Second Opinion Network aims to be a useful "problem-solving" support revisiting each diagnostic and therapeutic step and properly re-addressing tailored treatments and prognoses, as well as preventing unnecessary investigational procedures and unhelpful and expensive medical and surgical interventions **[8]**.

All the patients were visited and informed during a personal interview, gave their permission, and signed an informed consent.

The UDCA perfusion schedule was standardized to 3500 gr/UDCA infused each other day for a total of 10 sessions in 3 weeks. Nausea and vomiting were recorded daily on a diary card while quality of life was assessed, before treatment and at the end, using the Rotterdam Symptom Checklist (RSCL) questionnaire. We evaluated asthenia, weakness, heaviness and pain in the right hypochondrium biliary colics, post- prandial somnolence, nocturnal insomnia, reflux, meteorism and belching, constipation symptomatic hemorrhoids, itching, and skin eruptions, dermographism. The scores given in the RSCL Symptom Checklist are 1 (not at all), 2 (a little), 3 (quite a bit), 4 (very much): the higher the score, the higher the symptoms intensity and poor life quality.

III. RESULTS

The results showed an overall fair response of the liver insufficiency symptoms with parenteral treatment, and the functional lab exam markedly improved as well, especially transaminase, and bilirubin **(TABLE 1, FIG.1)**. Albumin synthesis also was variably increased as expression of liver cells metabolism re-activation **(FIG.2)**. The positive response to intravenous UDCA delivery was observed either in the chemo-intoxicated patients, or in multi metastatic liver colonization and largely depended by the amount of not invaded liver parenchyma.

The life quality evaluated by the RSCL score changed from 0 to 4 **(FIG.3).**

The lab exams were improved as well paralleling the energy recovery **(TABLE 1)**. No side effects have been detected during the therapy.

ISSN No:-2456-2165

TAB.1 LIVER PARAMETERS IN PARENTERAL BILE SALTS THERAPY

N.	PAT.	AGE (yrs)	CANCER TYPE	Aspartate transaminase - AST (U/L), range (8-48)		Alanine transaminase -ALT (U/L) range (7-55)		Alkaline phosphatase - ALP (U/L), range (40-129)		Total protein (g/dL), range (6.3-7.9)		Gamma-glutamyl transferase-GGT (U/L), range (8-61)		Bilirubin (mg/Dl), range (0.1-1.2)		Albumin (g/DL), range (3.5-5)	
				PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST	PRE	POST
#1	B.L.	55	Sigmoid cancer of 2 years before. Liver metastasis	180	62	118	75	150	101	8.5	6.3	91	61	5.1	1.8	4	5
#2	D.A.	40	Obstruction and perforation due to colorectal cancer, colostomy. Liver metastasis	150	75	102	60	168	99	8.9	6.6	93	60	4.2	1.5	3.5	5.1
#3	S.A.	70	Right-sided colorectal cancer (RCRC) 5 years ago. Liver metastasis	195	51	156	58	191	57	9.2	7.1	101	64	5.0	1.0	2.9	4.9
#4	T.V.	80	Esophageal cancer. Radiotherapy, chemotherapy, mediastinal metastasis	105	63	120	55	157	40	9.1	7.3	110	59	4.9	1.0	4.1	5
#5	S.A.	51	Bladder cancer , cystectomy,peritoneal relapse, chemotherapy	130	79	170	43	173	71	9.3	6.8	121	63	4.4	1.1	3.7	4.8
#6	M.C.	44	Ovarian cancer, lymph nodes and liver metastasis	140	24	153	52	168	52	9.4	6.4	134	67	3.9	1.4	3.4	5
#7	O.T.	43	Gastric cancer, Krukenberg tumor	169	29	107	67	150	49	8.1	7.2	133	55	4.6	1.3	3.1	4.6
#8	B.M.G	62	Pancreatic cancer liver diffusion	158	12	173	62	141	60	8.5	6.8	128	43	4.9	1.2	2.9	4.3
#9	B.D.	56	Gastric cancer, chemotherapy	198	14	195	30	137	54	7.8	6.9	98	41	4.0	1.6	3.1	4.8
#10	G.G.	58	Malignant centroblastic lymphoma, high aggressive chemotherapy	110	30	109	39	120	62	8.7	7.6	99	23	4.0	1.8	2.2	3.9
#11	P.I.	61	Massive gastric cancer, chemotherapy	170	48	165	56	127	42	10.5	7.9	121	18	4.3	1.5	3.1	5
#12	A.A.	61	Synchronous breast and colon cancer with biliary and liver metastasis	122	51	105	42	139	63	11	8.3	139	52	4.1	1.1	2.8	4.5
#13	M.G.	55	Esophageal cancer, unable to treat with chemotherapy	178	50	179	52	167	81	9.9	7.9	141	32	4.7	1.5	3.2	4.2
#14	P.M.	55	Rectal cancer, liver metastasis	115	49	153	44	188	49	9.5	8.6	157	31	5.0	1.5	4.0	5
#15	S.E.	62	Colon Cancer , high dosage chemotherapy	112	73	168	47	199	96	12.5	8.2	168	29	3.9	1.2	2.5	2.9
#16	B.S.	63	Carcinoma of the transverse colon, Liver and lung metastases	105	57	165	51	203	72	8.8	6.3	181	13	4.9	1.3	2.9	3.7
#17	L.L.	31	Duodenal cancer, Krukenberg's tumour, 18 Oxaliplatin therapy, high dosage	140	83	160	48	179	102	9.1	7.1	189	10	4.7	1.1	3.0	5
#18	M.V.	71	Rectal cancer, colostomy, diffuse metastasis	107	53	137	69	210	113	8.7	6.9	191	29	5.0	1.1	3.1	4.8
#19	C.G.	67	Rectal and lung cancer, liver metastasis	103	70	147	72	160	95	8.3	7.3	137	12	4.8	1.7	3.2	4.3
#20	B.N.	51	Ovarian cancer, chemotherpay, diffuse metastasis	169	87	159	40	182	126	8.2	6.8	164	31	4.7	1.5	3.9	4.9
#21	B.D.	63	Gallbladder cancer with liver invasion	186	36	149	35	220	104	7.7	7.3	149	12	4.6	1.5	3.1	5
#22	E.E.	45	Gastric cancer	170	29	152	29	173	53	13.4	7.8	135	11	4.9	1.4	3.8	4.6
#23	G.A.	72	Colon cancer with diffuse metastasis	188	52	196	31	164	47	12.9	8.1	127	24	4.8	1.5	3.9	4.3
#24	C.D.	80	Gallbladder cancer with direct liver infiltration	105	69	193	27	137	58	11.3	7.7	110	19	5.0	1.7	4.1	5.1
#25	M.B.A	45	Gastric cancer + krukenberg	192	53	188	19	164	63	15.9	9.1	124	48	4.7	1.6	2.7	3.9
#26	C.C.	58	Colon and gastric cancer with liver peripheral involvement	179	45	170	25	182	76	14.2	7.6	130	38	4.5	1.8	3.4	4.7
#27	D.A.	52	Pancreatic cancer speading into epiploon and liver intrarterial chemotherapy	109	83	182	58	219	88	13.1	6.7	113	42	5.0	1.2	2.8	4.1
#28	C.O.	62	Liver metastasis from colon cancer	194	76	183	62	195	51	8.9	6.2	107	18	4.9	1.2	4.00	5
#29	P.G.	43	Gastric cancer with esophageal inoperable stricture	176	59	195	51	192	63	11.3	6.9	118	57	4.8	1.5	3.9	4.7
#30	R.S.	75	Rectal cancer with bone and liver metastasis	171	49	174	46	206	92	12.7	7.3	126	42	4.75	1.5	3.8	4.4
#31	P.N.	47	Hodgkin lymphoma, high dose chemotherapy toxicity	114	92	199	42	199	78	10.4	6.9	119	37	4.99	1.7	2.9	4.8
#32	T.E.	67	Gastric cancer, liver metastasis	83	42	196	39	160	49	16.2	9.3	129	22	4.56	1.7	2.5	4.3
#33	M.G.	54	Right colon, liver metastasis	75	52	189	33	152	56	12.2	9.8	108	28	4.91	1.4	3.9	4.5
#34	S.E.	61	Pancreatic cancer	69	38	142	42	173	53	11.4	9.2	98	15	5.01	1.1	2.3	4.9
#35	S.G.	69	Liver metastasis, Prostate cancer	89	42	128	52	185	57	10.7	8.5	105	11	4.96	1.5	4.1	5
#36	P.M.	80	Pancreatic cancer	58	29	111	31	196	49	9.9	8.7	94	34	4.8	1.0	3.8	4.3
#37	G.L.	73	Pancreas distal cancer, liver metastasis	108	71	108	29	157	58	10.1	7.3	112	29	4.6	1.3	2.8	4.9
#38	S.C.	80	Rectal cancer, liver metastasis	73	16	102	44	196	63	8.9	7.1	165	21	4.2	1.0	3.7	4.8
#39	A.M.	65	Ovarian cancer, toxicity by adriamicin 60mg + taxol 174.5 mg 7 kg	149	83	108	39	208	75	14.3	8.3	110	35	4.0	1.5	2.9	4.3
#40	R.E.	62	Gastric and liver metastasis	90	42	129	55	169	45	12.1	7.9	98	10	3.9	1.55	3.9	4.5
#41	P.R.	65	Pancreas cancer, biliary stent	101	39	116	62	147	49	17.9	7.7	105	55	4.5	1.5	4	5
#42	F.T.	41	Mandible cancer with infiltration of the hypopharynx	170	95	105	67	217	79	13.3	7.3	99	58	4.9		2.7	4.1
#43	B.B.	67	Gastric cancer with liver metastasis	109	86	107	29	189	73	12.0	8.2	118	62	5.0	1.7	2.6	4.8
#44	G.V.	64	Lung cancer	168	40	128	17	197	84	11.7	7.0	137	54	4.8	1.4	3.2	4
#45	P.L	58	Left colon cancer, liver metastasis	171	29	125	35	182	59	10.4	7.4	107	46	5.0		3.3	3.9
#46	P.G.	51	Ovarian cancer, taxol + carboplat. toxicity	154	82	117	27	179	62	10.2	6.6	139	39	4.9	1.1	2.9	3.8
#47	A.E.	62	Previous mastectomy, lung pleura and liver metastasis 5 years later	109	71	112	63	198	79	13.4	6.2	146	17	5.0	1.2	2.0	4
#48	B.L.	69	Sigmoid cancer, lymph node and liver metastasis	107	65	195	40	206	66	11.3	6.4	102	11	4.6	1.9	3.8	4.9
#49	P.T.	68	Rectal cancer liver metastasis	155	49	167	51	198	86	11.1	6.4	96	8	4.9	1.5	2.9	4.5
#50	A.C.	57	Ovarian metastasis, retroperitoneal	167	24	181	48	186	91	10.5	6.8	119	14	4.85	1.2	2.8	4.8

ISSN No:-2456-2165

#51	M.C.	47	Metastasis from dorsum melanoma	189	38	135	39	191	72	9.9	7.1	102	58	5.3	1.5	4.1	4.5
#52	G.G.	55	Abdominal rhabdomyosarcoma with liver infiltration	192	45	192	20	205	79	12.1	8.0	110	42	4.9	1.8	3.9	4.1
#53	M.L.	61	Esophageal cancer	143	20	165	28	178	62	11.9	7.7	98	30	5.1	1.9	2.8	4.9
#54	B.S.	63	Colon cancer	171	17	189	41	199	77	13.4	8.9	123	37	4.6	1.6	4.0	5.1
#55	B.L.	61	Liver metastases from choriocarcinoma	160	56	145	47	201	56	12.3	9.2	103	22	4.1	1.4	3.7	3.9
#56	L.L.	31	Gastric cancer + krukenberg	148	8	162	61	177	71	9.6	7.9	112	13	3.9	1.31	3.6	4.5
#57	P.M.	29	Liposarcoma liver toxicity	182	10	185	38	192	85	10.1	6.8	127	18	5.2	1.6	2.8	4.1
#58	B.F.	62	Colorectal cancer	193	24	142	33	156	92	9.8	6.2	139	21	4.8	1.2	4.1	4.9
#59	C.L.	56	Rectal cancer, liver metastasis	159	32	103	27	171	82	10.5	6.1	144	39	5.6	1	3.7	5.1
#60	A.P.	48	Gastric cancer with liver and lung metastasis	144	17	167	19	183	79	11.2	7.2	156	45	5.1	1.9	3.8	4.0
#61	C.G.	68	Rectal cancer, peritoneal and liver invasion	133	19	199	21	189	50	9.9	5.8	161	40	4.9	1.7	3.7	4.1
#62	C.A.	51	Liver metastases from kidney cancer	128	22	188	11	149	42	10.1	6.2	149	32	4.4	1.2	3.6	3.9
#63	P.A.M	65	Esophageal cancer	152	34	193	19	172	57	9.9	5.9	172	26	4.6	1.52	2.9	3.5
#64	F.G.	67	Gallbladder cancer	159	38	165	26	170	62	8.8	6.9	167	29	5.7	1.9	2.8	4.1
#65	R.M.	53	Gastrectomy, subostruction chemotherapy	171	35	101	21	179	70	8.2	6.2	152	37	5.1	1.6	3.4	3.9
#66	M.R.	57	Ovarian cancer, toxicity by adriamicin 60mg + taxol 174.5 mg 7 kg	163	41	113	38	192	61	7.9	6.3	145	42	3.8	1.8	4.1	5
#67	L.L.	62	Bladder cancer , with bone and liver metastasis	196	14	152	33	193	51	8.5	6.6	129	48	5.0	1.0	3.6	4.9
#68	C.C.	58	Gastric Cancer	167	20	118	42	199	40	8.3	9.8	117	51	4.2	1.3	2.7	3.8
#69	S.E.	43	Gastric Cancer extended to left hepatic lobe	173	19	127	48	178	43	7.8	6.3	114	59	3.7	1.4	3.9	4.2
#70	G.A.	72	Colon cancer, diffuse liver metastasis	187	21	131	51	188	52	8.2	6.7	137	67	4.9	1.5	3.8	4.4
#71	B.L.	68	Gastric cancer, liver metastasis	159	29	142	40	167	48	7.4	6.9	124	51	5.3	1.5	4.1	5
#72	F.B.	48	Pancreatic tail cancer, spleen and liver metastasis	104	13	151	31	178	44	7.6	6.4	99	42	4.3	1.8	3.7	4.1
#73	G.M.	52	Pancreatic Cancer liver infiltration	116	9	167	28	188	56	6.7	7.6	105	30	5.6	1.0	3.9	4.3
#74	G.L.	71	Colon cancer, liver metastasis	129	11	182	22	160	78	6.2	6.2	129	48	3.9	1.2	3.5	4
#75	E.L.	42	Abdominal rhabdomyosarcoma, visceral metastasis	111	27	155	18	168	62	6.9	6.1	118	56	4.1	1.81	3.4	3.9
#76	T.E.	66	Gastric cancer, liver metastasis	189	35	123	33	179	68	7.5	6.3	134	61	5.7	1.6	3.2	4.2
#77	S.L.	57	Colon cancer, liver metastasis	167	12	181	51	193	59	8.5	6.7	159	70	4.2	1.8	3.5	4.5
#78	M.L.	49	Colon cancer, liver metastasis	178	23	179	48	192	45	9.1	6.4	132	52	5.0	1.9	2.6	4
#79	C.O.	75	Adrenocortical carcinoma, liver metastasis	134	29	157	39	206	51	10.1	6.4	120	49	3.8	1.5	2.9	4.1
#80	C.F.	61	Breast cancer, bone and liver metastasis	165	15	163	32	210	59	10.5	6.5	136	41	5.1	1.3	3.9	4.2
#81	S.E.	60	Pancreatic cancer, stent and duodenal infiltration	181	32	128	25	209	64	9.9	6.1	151	20	4.6	1.7	3.8	4.5
#82	G.M.	81	Gastric cancer with bowel obstruction	167	9	141	17	189	75	8.9	8.7	149	24	5.2	1.9	2.6	3.9
#83	C.N.	51	Gastric peritoneal carcinomatosis	172	12	112	39	188	82	7.5	8.2	147	19	4.5	1.5	3.9	4.6
#84	S.M.	80	Pancreatic cancer	160	45	106	26	171	44	9.3	7.0	138	16	5.0	1.45	3.7	5
#85	G.A.	37	Thyroid, colon cancer, liver metastasis	127	32	101	18	177	40	10	6.7	127	10	3.6	1.9	3.6	4.2
#86	B.B.	74	Recurrent Colon Cancer	122	28	158	12	165	46	8.0	7.2	119	23	4.1		3.6	4.5
#87	G.A.	72	Gastric Cancer extended to left hepatic lobe	106	23	146	25	159	52	11.1	6.2	120	33	3.9	1.3	2.9	3.9
#88	M.M.	52	Ovarian cancer, toxicity by adriamicin + taxol	117	18	139	37	160	63	10.6	6.7	115	17	4.0	1.6	4	5.1
#89	S.M.	67	Massive gastric cancer, chemotherapy	187	11	124	48	162	65	9.10	6.9	109	28	3.8	1.5	4.1	4.9
#90	P.A.	48	Hodgkin lymphoma, high dose chemotherapy toxicity	146	37	161	39	159	58	8.8	6.67	111	40	4.7	1.7	3.9	5.1
#91	N.M.	58	Ovarian cancer, lymph nodes and liver metastasis	132	29	155	11	161	62	7.9	6.2	128	11	5.9	1.2	2.7	4.4
#92	A.F.	63	Colon Cancer , high dosage chemotherapy	105	18	149	18	160	69	8.3	6.5	115	18	5.6	1.4	2.7	4.7
#93	C.G.	54	Left colon cancer, liver metastasis	109	12	137	8	153	48	7.8	6.9	110	32	4.0	1.8	3.4	4.0
#94	G.E.	62	Hodgkin lymphoma, high dose chemotherapy toxicity	167	44	120	17	178	50	8.1	6.7	148	28	3.8	1.4	3.6	4.1
#95	C.G.	68	Pancreatic cancer speading into epiploon and liver intrarterial chemotherapy	182	37	116	20	185	56	11.2	9.2	161	31	4.2	1.7	3.9	4.3
#96	L.A.M	65	Duodenal cancer, Krukenberg's tumour, 18 Oxaliplatin therapy, high dosage	178	23	131	12	192	42	10.2	8.8	94	48	4.8	1.8	3.4	4.6
#97	L.P.	70	Left colon cancer, liver metastasis	155	13	199	34	167	51	11.7	7.5	104	28	5.4	1.4	2.4	4.9
#98	G.A.	77	Ovarian cancer, taxol + carboplat. toxicity	103	9	175	10	159	67	9.9	6.3	108	35	5.9	1.6	2.9	3.8
#99	L.L.	58	Colon cancer with diffuse metastasis	118	17	147	21	169	43	10.2	5.8	117	49	5.2	1.9	2.3	3.7
#100	L.G.	63	Liver metastasis from colon cancer	176	41	142	9	172	40	9.7	6.6	159	17	5.1	1.2	4	5

Table 1:- Liver parameters in parenteral bile salts therapy

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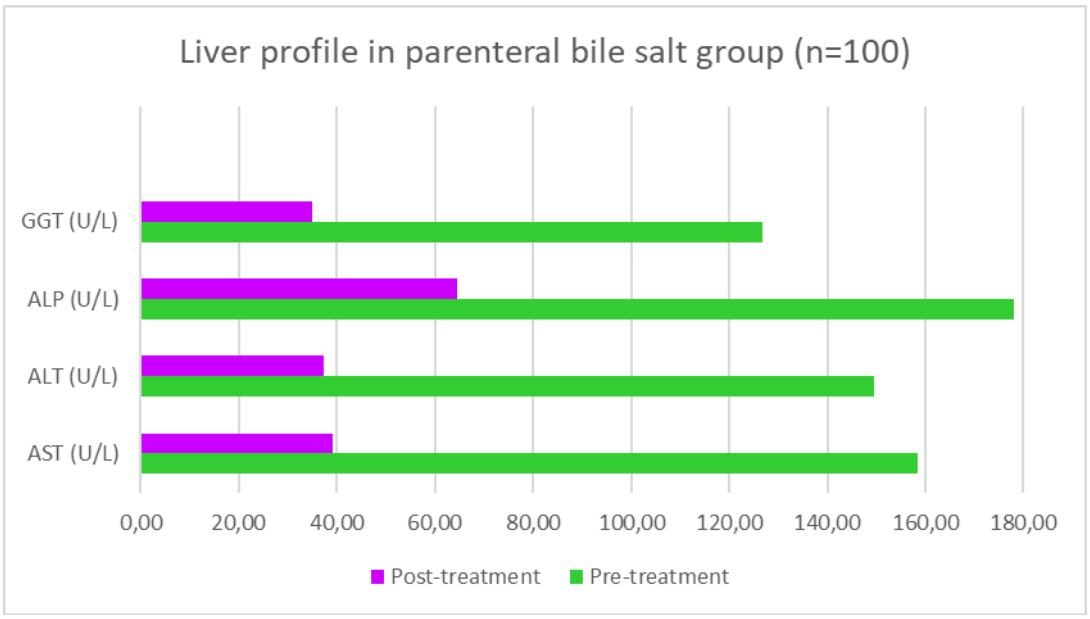

Fig 1:- Graphic representation of clinical parameters in patients with parenteral treatment

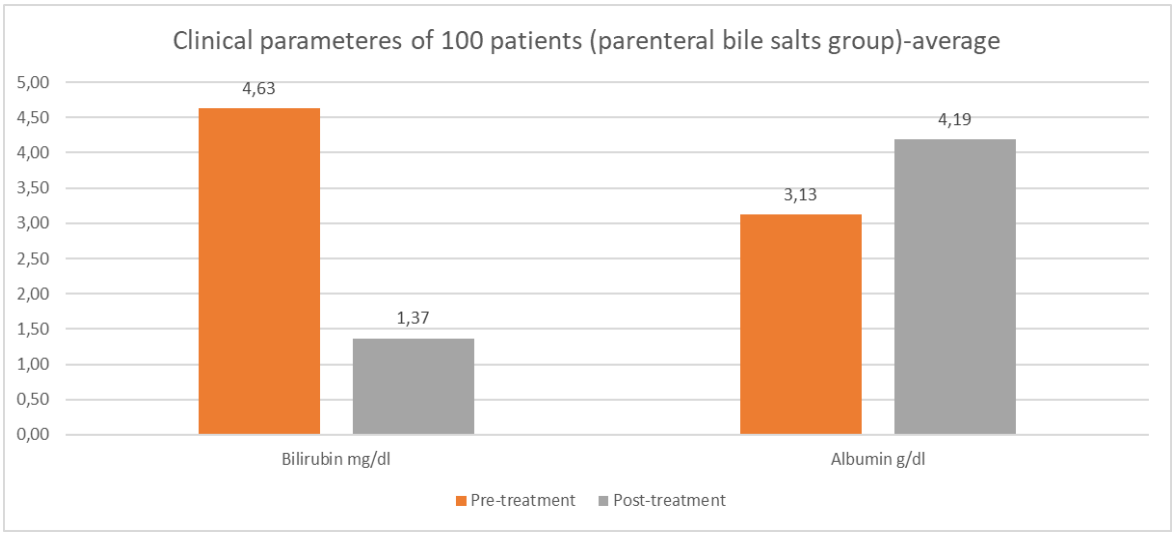

Fig 2:- Graphic representation of bilirubin and albumin value in parenteral bile salts group (n=100 patients)

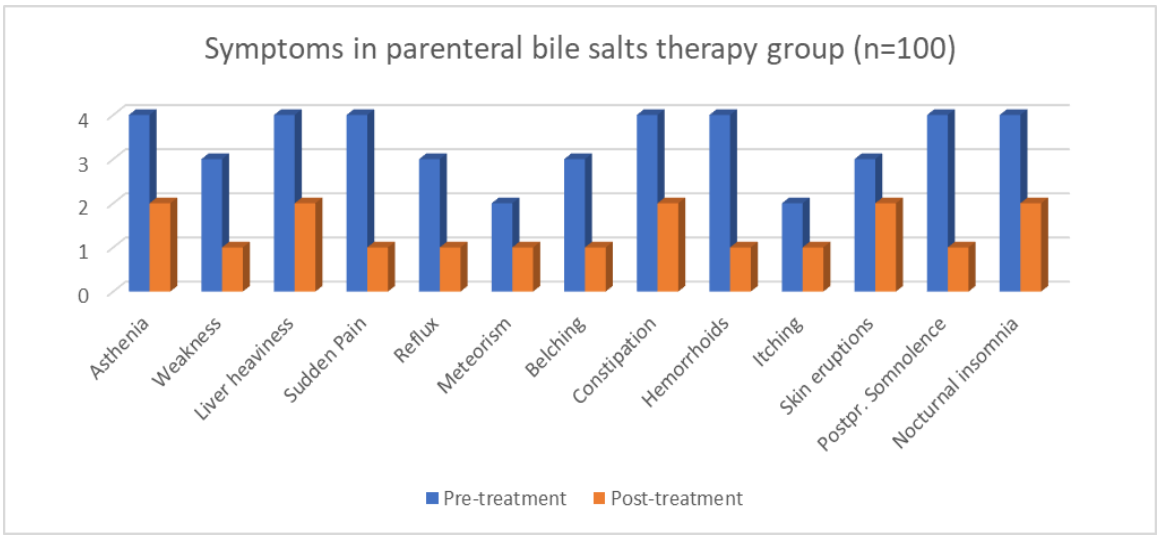

Fig 3:- Graphic representation of symptoms in parenteral bile salts therapy group before and after treatment

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IV. DISCUSSION AND CONCLUSIONS

The patients affected by cancer with gut function impairment, and liver dysfunction due either to chemotherapy toxicity, liver metastasis, or paraneoplastic effects have a very poor life quality that can effectively be improved by administration of biliary salts via parenteral route, because the oral delivery wouldn't reach adequate absorption rate and would potentially generate adverse effects.

In our case series we observed after the third intravenous infusion, a quick improvement of the symptoms, especially asthenia, post- prandial somnolence, insomnia, reflux and meteorism heaviness in the right hypochondrium, biliary colics, itching, skin eruptions, dermographism etc **(FIG.2).**

The intermittent treatment with intravenous bile salts is thus advisable and can also maintain the enterohepatic circle notwithstanding the intestinal problems and the bad nutritional conditions, and in prolonged starvation and total parenteral nutrition it prevents also the stones formation.

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