

Case Reports of Cancer Patients with Hepatic Metastases Treated by Standardized Plant Immunomodulatory Preparations

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Abstract: *Background:* Metastatic hepatocellular carcinoma often has a multifocal tumor pattern with markedly depressed hepatic function. Hepatic resection in many cases results in no long-term benefit. After a chemotherapy hepatic tumors rarely disappear completely and the duration of responses is short. In the last decades growing evidence suggested that a disturbed balance in the innate system can also play a role in the poor prognosis of hepatic tumors.

Objectives: The aim of this article is to present and discuss several favorable clinical responses of patients with hepatic metastases who parallel to conventional oncologic therapy, were treated with immunologically effective and standardized plant extracts.

Course of Therapy and Results: In accordance with the bell-shaped dose-response relationship of mistletoe lectins (MLs), the patients were treated with a fermented mistletoe extract (ME) preparation, standardized for the active sugar-binding lectin contents. Thus, an optimal dose between 0.5 and 1.0ng/kg MLs was given twice a week subcutaneously. In addition to ML therapy, a heteropolysaccharide rice bran preparation standardized for arabinoxylan (12-45mg/kg MGN-3/Biobran^R twice a week) and wheat germ extract (WGE) standardized for 2, 6-dimethoxy-p-benzoquinone (50-80mg/kg Avemar^R four times a week) was also given. In these case reports the clinical progress of seven patients showed a complete or nearly complete remission of hepatic metastases.

Conclusion: ML, MGN-3 and WGE seem to be potent candidates to be regarded as a supportive therapy to surgery, hormone treatment or chemotherapy for patients with hepatic metastases. These case reports require further clinical studies.

Keywords: Hepatic metastasis, immunomodulation, mistletoe extract, mistletoe lectin, arabinoxylan, MGN-3, wheat germ extract, benzoquinone.

INTRODUCTION

The prognosis for patients with primary or metastatic hepatocellular carcinoma is negatively correlated with jaundice, cirrhosis and metastases to other organs. Median survival was mostly found to be very short (four to six months). Operative procedures, which generally entail lobectomy or segmentectomy, are associated with considerably better survival rates [1]. However, most patients with hepatocellular carcinoma are not surgical candidates because of a multifocal tumor pattern or markedly depressed hepatic function, and hepatic resection in such cases results in no long-term benefit. Consequently, these patients are mostly treated with chemotherapy, which is sometimes able to induce reductions in the size of measurable tumors. However, chemotherapy rarely causes the tumor to disappear completely, and the duration of response is short.

In the last decades special attention has been focused on the role of the disturbed immune balance in the poor prognosis of metastatic tumors [2-8]. In this

article, several case reports of various tumor patients with hepatic metastases are presented who were treated with standardized plant immunomodulatory preparations in combination with conventional oncologic therapy modalities.. All patients received mistletoe extracts (ME) standardized in term of mistletoe lectins (ML) given in appropriate doses, which were shown to induce the most effective improvement in cancer-related disarray of the immune balance [9-12]. Parallel with ME therapy, two other standardized plant extracts with immunomodulatory effects were also given: a heteropolysaccharide preparation from rice bran standardized for arabinoxylan (BioBran/MGN-3) and fermented wheat-germ extract standardized for its 2, 6-dimethoxy-p-benzoquinone (2, 6-DMBQ) content (WGE / Avemar^R). Since these immunomodulatory treatments in combination with oncologic therapies resulted in more complete remission, their importance is discussed.

MATERIAL AND METHODS

Mistletoe Extract (ME) and its Standardization with Enzyme Linked Lectin Assay (ELLA)

Iscador^R is a fermented aqueous mistletoe plant extract manufactured and supplied by Weleda AG (CH-

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4144 Arlesheim, Switzerland). The active (sugar-binding) lectin content of commercially available mistletoe extracts was measured in the research laboratory of Pharmacochemical Department of Medical University Pécs.

The determination of sugar binding mistletoe lectins (MLs) level in ME was carried out by an optimized ELLA technique as published previously [13]. Briefly, the method is based on the binding of lectin to an immobilized oligosaccharide ligand (asialofetuin) and subsequent binding of specific (polyclonal) antibody to the bound lectin. The specific binding of rabbit antibodies was quantitatively assessed using goat anti-rabbit peroxidase and the subsequent generation of a colored product from the substrate phenyldiamine hydrochloride. Standard lectin was isolated from fresh plants using affinity chromatography and then it was lyophilized as described previously [13].

Dose of Standardized ME Preparations

Cellular responses of the innate immune system in Balb/c mice and in healthy volunteers induced by ME were repeatedly investigated. Standardized ME exhibited a bell-shaped dose-response relationship and 0.5- 1.0 ng/kg lectin doses were found to be most effective as it was always assessed previously using healthy volunteers. Since two and three therapy-free days were found to be necessary for an immunologically optimal effect, the subcutaneous ME injections were regularly given twice a week. Consequently, lectin oriented doses of ME applied in the treatment of patients corresponded to this regimen.

Doses of Standardized Rice Bran Extract (BioBran/MGN-3)

The second immunomodulator used in the combinative treatment of the presented patients is BioBran/MGN-3 which is manufactured and supplied by Daiwa Pharmaceutical Co, Ltd, Tokyo, Japan. BioBran/MGN-3 is composed of denaturated hemicellulose, which is obtained by rice bran hemicellulose reacting with multiple carbohydrate-hydrolyzing enzymes from shiitake mushrooms. BioBran/MGN-3 is standardized for its main chemical component: arabinoxylan with a xylose (in its main chain) and with an arabinose polymer (in its side chain). To the presented patients BioBran/MGN-3 was given per oral in doses between 12 and 45mg/kg twice a week parallel to the optimized, lectin-oriented ME therapy.

Application of Fermented Wheat-Germ Extract (WGE / Avemar^R)

WGE (trade name Avemar^R) is a complex of multiple, biologically active molecules obtained from fermented wheat-germ extract. Its biological effects are related to 2-methoxy-p-benzoquinone (2-MBQ) and 2, 6-dimethoxy-p-benzoquinone (2, 6-DMBQ) in the form of glucoside. During the fermentation the quinones are released by the glucosidase enzyme of the yeast fungus. The 1045 mg tablets are manufactured and supplied by Biopharma Kft, Kunfehértó, Hungary. WGE is standardized for its 2, 6-DMBQ content (0.4 mg/g concentration on dry matter basis). In presented cases WGE was given per oral in doses between 50 and 80 mg/kg/die four times a week (on the day of immunotherapy and 24h thereafter).

Eligibility Criteria of Patients with Hepatic Metastases

Inclusion criteria: 1. histological defined malignant tumor; 2. patients did not require nursing; 3. at begin of observation they did not receive morphine derivatives. Exclusion criteria: 1. no histological data; 2. Karnofsky index is less than 60; 3. undesired side effects (such as allergy).

Ethics Committee

Ethics committee proposed to observe and publish case reports of own patients treated by ME standardized in terms of lectin activity. All patients have given an informed consent to process and publish their dates. These case reports may stimulate an interest for other research groups according to the opinion of the ethics committee.

RESULTS

In Table 1 eight patients with hepatic metastases are listed according to the period of observation.

Case 1

In a 72-year-old patient, tumor extirpation of a malignant melanoma (IA SSM Clark level II, pT1 N0 M0, Breslow 0.375 mm) from the right upper arm was carried out in 1992, and because of a second nodular melanoma (IIA, pT3 pN0 pM0) on the right shoulder a second surgery was performed in 1999. In August 2001 three axillary lymph nodes (right) were removed. At the same time in segments 4/5 a solitary hepatic metastasis was detected. From October 2001 the

Table 1: Brief Summary of Eight Case Reports of Various Patients with Hepatic Metastases

	Primary tumor	Hepatic metastasis	Other metastasis	Immuno-therapy	Other therapy	Duration of observation	Clinical progress of hepatic metastasis
Case 1	Malignant melanoma	Solitary	Lymph Nodes	L	-	12 years	CR
Case 3	Breast cancer	Multiple Recidiv	LN + Ovarian	L L	Cycloph. Epir. 6x Letrozol Irradiation	20 mo 10 mo	CR PR
Case 4	Ovarian cancer	Multiple	-	L	6x Taxot. Carbopl.	31 mo	NC
Case 7	Sigmoid cancer	Operated multiple	-	L	FOLFOX 6x	49 mo	CR
Case 2	Breast cancer	Multiple	-	L+B+W	Hormone (Femara)	12 mo	CR
Case 5	Breast cancer	Multiple	-	L+B+W	Xeloda 2500mg/d.	11 mo	CR
Case 6	Colon cancer	Multiple	Retrop. LN-meta	L+B+W	Avastin FOLFIRI	4 mo	CR
Case 8	Colon cancer	Operated multiple	Mediast + abd. LN	L+B+W	FOLFIRI FOLFOX Avastin	31 mo	CR

Abbreviations: L = 0.5-1.0mg/kg mistletoe lectin given in standardized mistletoe extract twice a week; B = 12-45 mg/kg MGN-3/Biobran standardized for arabinosyl (twice a week); W = 50-80 mg/kg wheat germ extract standardized for 2, 6-dimethoxy-p-benzoquinone (four times a week); LN = lymph nodes; FOLFOX = Oxaliplatin + Leukovorin+ 5-Fluorouracil; FOLFIRI = Leukovorin+ 5-Fluorouracil. CR=complete remission; PR= partial remission; NC= no change.

patient was given lectin-standardized ME therapy. In June 2002 a complete remission of liver metastasis was established. Until 2012 no recurrence of the liver metastasis and normal liver functions were regularly observed. The patient quality of life has been excellent.

Case 2

In a 59-year-old patient nine years after a breast cancer operation (left) an extensive local recurrence of a multifocal, invasive ductal carcinoma was removed by surgery in November 2011. At the same time multiple hepatic metastases in the right lobe of the liver with extents up to 35 mm were detected sonographically. In November 2011 lectin-oriented ME therapy was started together with MGN-3/Biobran and WGE. Parallel to this immunomodulatory treatment an anti-estrogen therapy (20 mg Femara/die) was also given. In January 2012 PET/CT and sonography could not find any hepatic metastases. Liver functions were also normal. Further control investigations in June 2012 and in November 2012 have pointed to complete remission.

Case 3

In the now 47-year-old patient the first diagnosis of breast cancer (cT4b cN3 M1) with multiple hepatic metastases (in segment 4a/b) took place in March 2009. From April 2009 until September 2009 the patient was given six cycles Epirubicin and Cyclophosphamide together with hormone therapy (Letrozol). At the same time she was regularly treated with lectin-standardized ME. After a partial remission of hepatic metastases an ablation of the breast was carried out in October 2009. Following the operation the patient was given an irradiation with 54 GY. Thereafter the patient received only a hormone therapy together with lectin-standardized ME, and in June 2010 a complete remission of the hepatic metastases was established in PET/CT. In June 2011 the hepatic metastases were renewed in PET/CT but only in a small degree. In April 2012 the patient was given a TARE-therapy (superselective radioactive ray treatment in segment 4a/b and segments 1 and 2). In May 2012 another nearly complete remission was again found accompanied by excellent quality of life.

The patient has been able to work 100% in her job and in her family.

Case 4

In the now 66-year-old patient an ovary carcinoma (pT3c pN1 M0) was removed by surgery in August 2005. Following the operation the patient was given six cycles Taxotere and Carboplatin. In November 2007 multiple hepatic metastases were detected in PET/CT. From November 2007 until April 2010 lectin-standardized ME therapy together with chemotherapy (Caelix and Gemzar, later Xeloda and Uromitexan) was given. In the course of 30 months no progression of her disease was observed.

Case 5

Because the now 49-year-old patient had ductal mammary carcinoma [T2 N1 (3/17) Mx], a tumorectomy in January 2010, and subsequently a hormone treatment (Femara) and chemotherapy (six cycles epirubicin and docetaxel) were carried out. In April 2011 multiple hepatic metastases were detected in PET/CT. In December 2011 seven liver metastases

were removed by surgery. Six weeks later a considerable progression of hepatic metastases was established in PET/CT. Because of the bad liver functions only a mono-chemotherapy with reduced dose (2500 later 1500 mg Xeloda /day) was given. In the same time an immunomodulatory treatment with lectin-standardized ME, MGN-3/Biobran and WGE was started. In April 2012 a considerable remission of the hepatic metastases (only three small metastases) were detected in CT (Figure 1). The liver functions have been normalized. From January 2012 until July 2012 the tumor markers decreased: carcinoembryonic antigen (CEA) from 36.1 to 2.95 ng/ml and the tissue polypeptide antigen (TPA) from 232 to 56.3 U/l (Figure 2). A rapid improvement of liver functions was summarized in Figure 3. In August 2012 a nearly complete remission of the hepatic metastases could be established. (The metastases were not measurable in CT). So far the quality of life has been excellent; the patient has been able to work 100%.

Case 6

In the now 63-year-old patient, a tumorectomy and a revision of regional lymph node metastases were

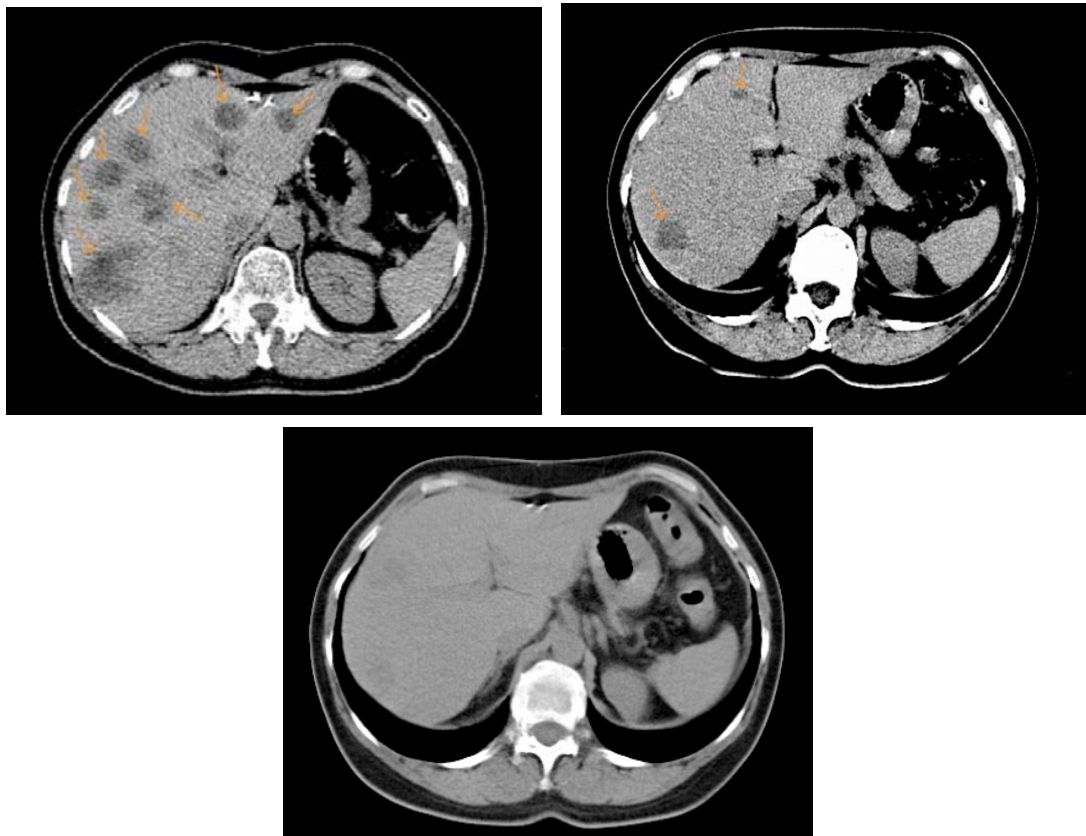
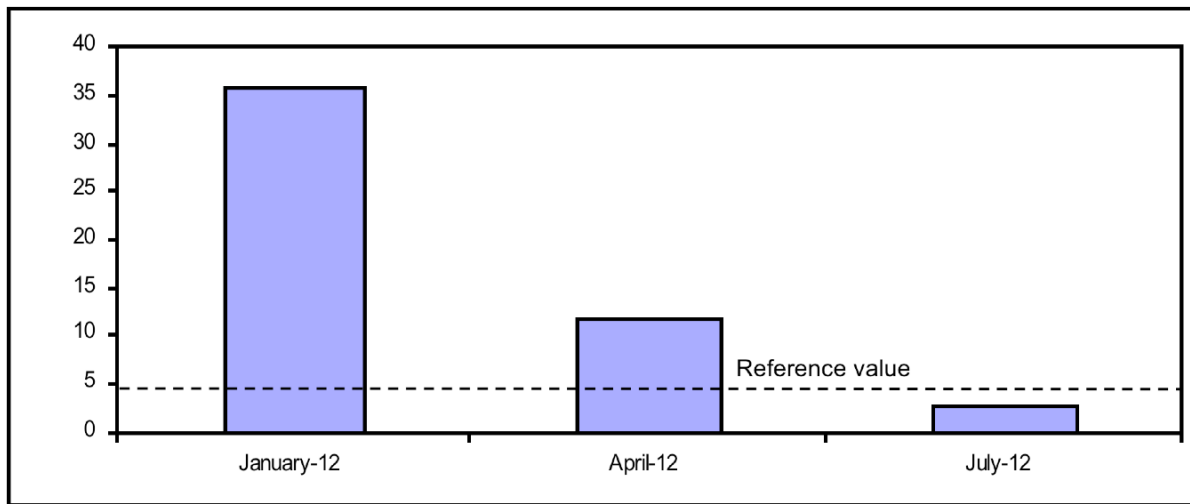
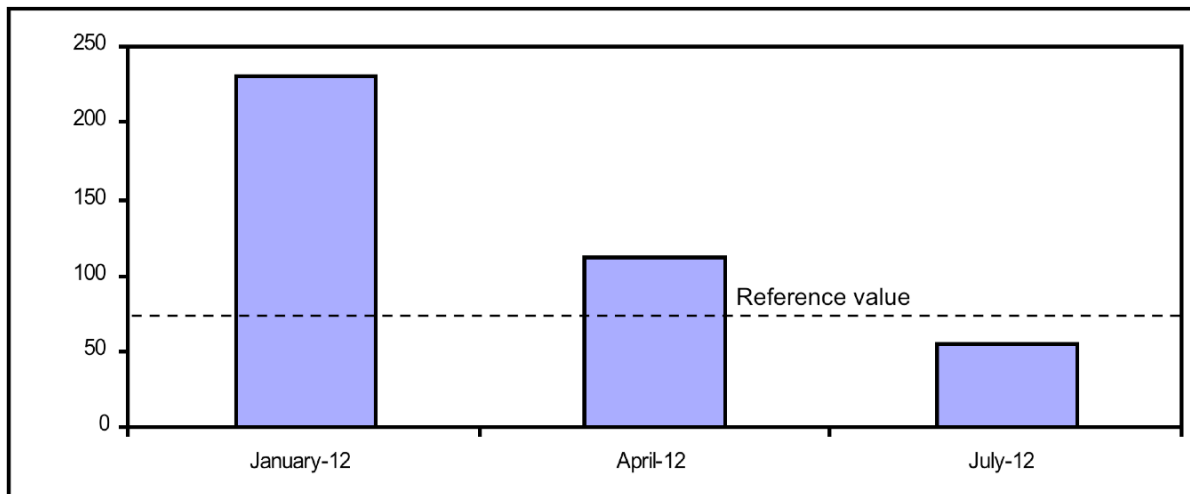


Figure 1: Computed tomography (CT) scans of hepatic metastases in a patient (case 5) who had a partial remission after three months and a complete remission after 8 months. She was treated with low doses of Xeloda (1500 - 2500 mg/die) combined with ME/ML, MGN-3/Biobran and WGE.



A



B

Figure 2: A. Carcinoembryonic antigen (CEA) values of patients (case 5) with hepatic metastases prior to therapy and during a treatment with low doses of Xeloda (1500 - 2500 mg/die) combined with ME/ML, MGN-3/Biobran and WGE. (Reference values: 0-4).

B. Tissue polypeptide antigen (TPA) values of patients (case 5) with hepatic metastases prior to therapy and during a treatment with low doses of Xeloda (1500 - 2500 mg/die) combined with ME/ML, MGN-3/Biobran and WGE. (Reference values: 0-75).

carried out in November 2010 because of metastatic colon carcinoma [Dukes C, T3 N1 (3/5) M1]. In the same time multiple hepatic, retroperitoneal and mesenteric lymph node metastases were established in PET/CT. From December 2010 until July 2011 the patient was given 12 cycles FOLFIRI (Leukovorin+ 5-Fluoruracil) with Avastin and Irinotecan. In July 2011 a progression of hepatic and lymph node metastases was observed in PET/CT. From August 2011 an immunomodulatory treatment with lectin-standardized ME, MGN-3/Biobran and WGE was given. As further oncotherapy only Avastin was parallely applied. In October 2011 no hepatic and no more lymph node metastases were established in CT. In November 2011

the immunomodulatory treatment was broken off and the patient died after a rapid progression in September 2012.

Case 7

Because of a metastatic sigmoid carcinoma [pT4 pN1 (13/35) M1] a hemicolectomy was carried out in June 2004 in a now 54-year-old patient. Following the operation six cycles FOLFOX (Oxaliplatin + Leukovorin+ 5-Fluoruracil) were given, and in December 2004 a liver segment resection was carried out. From August 2004 lectin-standardized ME therapy was applied. Until her death in July 2008 no recurrence

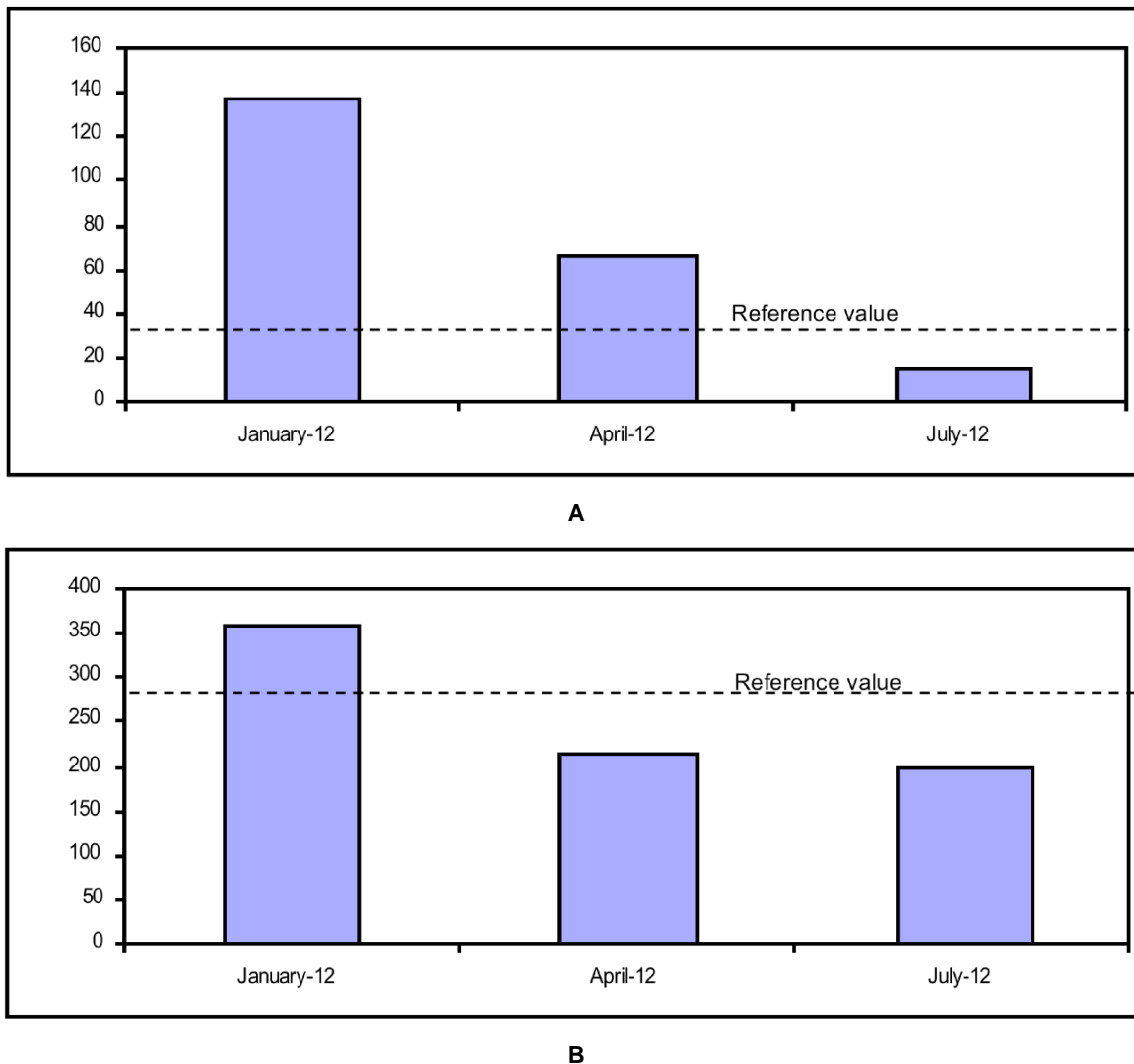


Figure 3: A. Gamma-glutamyltranspeptidase (gamma-GT) values of patients (case 5) with hepatic metastases prior to therapy and during a treatment with low doses of Xeloda (1500 - 2500 mg/die) combined with ME/ML, MGN-3/Biobran and WGE. (Reference values: 7-35 U/l.)

B. Alkaline phosphatase values of patients (case 5) with hepatic metastases prior to therapy and during a treatment with low doses of Xeloda (1500 - 2500 mg/die) combined with ME/ML, MGN-3/Biobran and WGE. (Reference values: 98-280 U/l.)

of hepatic metastases was observed in spite of a surgical operation because of an adnex metastasis in January 2007. The patient died following new lymph node and lung metastases.

Case 8

In the now 56-year-old patient a colon carcinoma [pT4 N1 (4/13) M1] was removed by surgery in July 2009. Two months later (in September 2009) a resection of hepatic metastases was carried out. Following the surgical operation seven cycles FOLFIRI (Leukovorin+ 5-Fluoruracil) and Avastin parallel with lectin-standardized ME therapy were given. In May 2011 no hepatic metastases were detected in PET/CT. Because of enlarged mediastinal, abdominal and

retroperitoneal lymph node metastases from May 2011 until January 2012 eleven cycles FOLFOX (Oxaliplatin + Leukovorin+ 5-Fluoruracil) were given. From May 2011 the lectin-standardized ME therapy was combined with MGN-3/Biobran and WGE. CT investigations in October 2011, in January 2012 and in March 2012 could not detect hepatic metastases and the lymph node metastases showed a nearly complete remission with a good quality of life. Because of financial problems in April 2012 the patient stopped the immunomodulatory treatment.

DISCUSSION

These case reports suggest that standardized plant immunomodulators (ML-oriented ME, arabinoxylan-

standardized MGN-3/Biobran and 2, 6-dimethoxy-p-benzoquinone-standardized WGE) can be helpful in the oncologic treatment of hepatic metastases. The combination of these plant immunomodulators with conventional oncologic treatments can render possible complete remissions which are rarely attainable by oncologic therapies only. As mentioned, the patients with hepatic metastases after chemotherapy can rarely reach a greater reduction than 50%, and the responses are short.

The first case report (Table 1) represents a complete remission of a liver metastasis after a lectin-standardized ME therapy given only. Until now the patient has had no recurrence of the tumor with best quality of life after an observation for 12 years. On the base of this good clinical progress further patients with hepatic metastases were specially worked up. The liver metastases of case 2 and 3 showed a remission after a combined therapy of hormones (anti-estrogens) and immunomodulators. As is well known, anti-estrogens are able to inhibit the proliferation of mammary cancer cells and therefore it can be speculated that the effect of anti-tumor immune cells on tumor progression is enhanced by this hormone therapy. Similarly to anti-estrogens, cytostatic drugs with antiproliferative effects seem to be helpful for anti-tumor immunological mechanisms. Case report 4 can support this hypothesis since the progression of liver metastases under high doses of chemotherapy only was stopped following its combination with lectin-standardized ME therapy, but no remission was attained. Case report 5 shows an important and rapid remission of hepatic metastases (Figure 1) treated with low doses of mono-chemotherapy (Xeloda) and with standardized plant immunomodulators (lectin-standardized ME, MGN-3/Biobran and WGE). These observations suggest the hypothesis that under certain circumstances these immunomodulatory treatments combined with low doses of chemotherapy may be more effective than their combination with high doses of cytostatic drugs. Case report 6 shows that a combination of Avastin (VEGFR inhibitor) with these standardized plant immunomodulators can also induce a complete remission. In case report 6 it can be presumed that after a clinical success stopping these immunomodulatory treatments is not advisable since after a complete remission the patient did not continue the immune therapy and she died following a rapid progression after one year.

Case reports 7 and 8 represent patients whose hepatic metastases were removed by surgery. In case

report 7 prior to the surgical resection lectin-standardized ME therapy had been given for 5 months. Further clinical observations did not reveal a recurrence of hepatic metastases and the patient died on account of other metastases five years later. Therefore the question is arises, whether various metastases can react to this immunomodulatory treatment in different degrees? In spite of the fact that various tumor cells can exhibit different sensitivity to immune responses, a great tumor burden is always less susceptible for therapeutic influence. In case report 8 the patient received pre-operative chemotherapy with lectin-standardized ME preparation for six months. After a postoperative chemotherapy ME, MGN-3 and WGE were regularly given and 31 months after the liver operation no recurrence of hepatic metastases was observed. The last two case reports support the hypothesis that preoperative and postoperative treatments with these standardized immunomodulators may improve the prognosis of patients following a liver metastasis operation. In all presented cases the quality of life was beneficially influenced.

Growing evidence support that the effector cells of the innate immune system are committed in two directions: M1 macrophages and CD1a+ dendritic cells (DC1) generate IL-12, pro-inflammatory cytokines and activate cytotoxic effector cells (such as natural killer /NK/ and natural killer T /NKT/ cells) which are potent inhibitors of tumor growth. However, they are defective in tumor patients. Available information suggests that tumor-associated macrophages belong to a prototypic M2 population [5]. M2 generates IL-4 and IL-10 which facilitate the generation of Th2 cells and inhibit Th1 cells [6]. M2 macrophages affect inflammation, promote cell proliferation by producing growth factors and products of the arginase pathway, as well as promoting angiogenesis and tissue repair [5].

Tumor patients can have up to 40% more M2 peripheral monocytes than healthy individuals who have only 10% M2 monocytes [6]. Natural killer T (NKT) cells can also have a similar opposing effect. In cancer, NKT-1 cells are protective by producing IFN-gamma to activate M1 and DC1 dendritic cells which produce IL-12, NKT-2 cells primarily inhibiting tumor immunity [7] and these findings indicate an impaired balance of the innate immune system in cancer patients.

Consequently, learning to manipulate this balance along the regulatory axis may be critical to devising

successful immune therapies against cancer in advanced stages of the disease [8]. For ML a highly specific receptor, the CD75 ganglioside was described [14-15], which was found in the PRR on several effector cells of the innate immune system [15]. The existence of this PRR receptor may explain the selective binding capacity of neutrophils and monocytes to ML since this lectin can act as a Pathogen Associated Molecular Patterns (PAMP) similar to certain lectin-like receptors of microorganisms [13; 16]. This selective binding can explain why ML was found to enhance the IL-12/NK-mediated cellular immune responses improving the tumor-related disturbance in the balance of innate immune system [11].

Similar to ME modulation, modified arabinoxylan from rice bran was also found to stimulate the type-1 cells in the innate immune system, such as human NK cell activity *in vivo* and *in vitro* [17] and phagocytic function by macrophages [18]. Its simultaneous administration with lectin oriented ME therapy renders possible an additive effect.

Standardized wheat germ extracts contain 2, 6-DMBQ in 0.4 mg/g concentration on dry matter basis [19]. The original perception originated more than 50 years ago by Albert Szent-Györgyi (discovery of vitamin C goes back also to him) [20]. *In vitro* and *in vivo* experiments with WGE revealed to a significant antimetastatic effect [20-22]. The combination of WGE with NK stimulatory substances, such as ML and arabinoxylan is promising since WGE induces a downregulation of major histocompatibility complex (MHC) class I proteins [23]. It is well known that decreased MHC I expression reduce the effect of killing inhibitor receptors (KIR) resulting in enhanced killing of tumor targets by NK cells.

Other biological properties of these plant preparations may also play a role in their beneficial effects, such as stimulation of apoptosis [12, 16, 19, 24] or inhibition of cell cycles in S phase [12, 19]. However, preclinical investigations in tumor models (using nude mice xenotransplanted with human leiomyosarcoma and interleukin-12-deficient C57BL6 mice) showed that without immunological reactions, these plant extracts induced less antitumor efficacy [25-26]. Preclinical data, previous case reports and preliminary clinical observations support these experimental results [9, 27-29].

Standardized plant extracts described above have a great advantage, they don't cause any side effects. In

terms of safety and toxicity of ME, available studies indicate that mistletoe therapy is well tolerated, and serious adverse events were not reported. Only a local reaction (erythema at the injection site after 8-10h) was observed in a percentage between 0.9 and 43 [30]. MGN-3 has also been judged to be a highly safe food as it was verified by conducting acute oral toxicity, mutagenicity, subacute toxicity, and antigenicity studies [31]. WGE has been put on the market as a non-toxic dietary supplement. Toxicological studies with high doses of WGE (3 g/kg) did not show any deviation from the controls [23].

CONCLUSIONS

Using standardized plant extracts, ML and arabinoxylan (which in previous studies have been shown to bind pattern recognition receptors on cellular components of the innate immune system improving the tumor-induced derangement of the natural immune balance) in combination with WGE may be helpful in the oncologic treatment of eight patients with hepatic metastases.

The aim of these case reports is to attract attention, and it is also clear that further clinical investigations are necessary.

DISCLOSURE STATEMENT

The authors declare that there is no competing or other conflicting interest in relation to this paper. The sponsor had no influence on the design or conduct of the study, interpretation of data or approval of the manuscript.

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