

Enhanced effectiveness of conventional oncotherapy with plant immunomodulators: Overview of recent advances

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ABSTRACT

There is growing evidence that tumor-associated immune imbalance is an important prognostic factor in several types of malignancy. Results from basic research as well as several case reports on sarcoma patients suggest that immune function may be improved by plant immunomodulators. Such treatments hold promise to partially restore the impaired balance along the regulatory access of the innate immune system that may be critical for clinical outcomes. There is also some evidence that combined therapy with plant preparations such as mistletoe extract injections with fixed *Viscum album* lectin content (0.5 to 1.0 ng/kg twice a week), rice bran preparation with a fixed dose of arabinoxylan (12 to 45 mg/kg twice a week) and wheat germ extract with a fixed dose of 2,6-dimethoxy-p-benzoquinone (50 to 80 mg/kg four times a week) on top of conventional oncotherapy may result in complete remission of hepatic metastases. These results suggest that the combination of these plant immunomodulators with conventional oncologic treatments can render possible complete remissions which are rarely attainable by oncologic therapies only. Studies using SF-36 questionnaires reported improved quality of life in advanced stages of various malignancies with plant-derived lectin immunomodulator. Combined therapy with plant immunomodulators, which are able to bind pattern recognition receptors on effector cells of innate immune system, may improve outcomes compared to conventional oncotherapy. However, further studies are required to provide additional evidence.

Keywords: Tumor, immune dysfunction, plant immunomodulator, *Viscum album* lectin, rice brain preparation, wheat germ extract.

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INTRODUCTION

The role of disturbed immune balance in the prognosis of patients with malignant tumors

Within the last decade, there has been increased attention focused on the prognostic significance of immune status in malignancy. Specifically, an altered balance in the innate immune system has been identified as an important clinical predictor. Decreased activity of

phagocytes and natural killer cells were identified as important features of cancer progression.

Several studies were undertaken to characterize this tumor-related immune imbalance identifying important mechanisms. These include disturbed balance between Th1 and Th2 immune responses and increased activity of regulatory T cells and myeloid-derived suppressor cells (Nagtegaal et al., 2001; Ostrand-Rosenberg and Sinka,

2009; Mantovani, 2007; Terabe and Berzofsky, 2008). Numerous studies have targeted the alterations of anti-tumor cellular immune response in various types of malignancy. In these studies, soluble factors were identified that are either produced or affected by malignant cells. In addition, enhanced suppressor activity of several lines of immunocompetent cells was also found to be an important factor in the development of the tumor-related immunocompromised state (Baskic et al., 2001).

It is now generally recognized that immunocompetent cells of the innate immune system are committed in two separate directions: (1) M1 macrophages and CD1a+ dendritic cells (DC1) generating IL-12 and other pro-inflammatory cytokines activating cytotoxic effector cells such as natural killer (NK) and natural killer T (NKT) cells, potent inhibitors of tumor growth; (2) prototypic M2 macrophages generating IL-4 and IL-10, which facilitate the generation of Th2 cells while inhibiting Th1 cells. Both of these two branches of innate immunity are affected by malignancy. The basic function of macrophages of the M2 type is to induce inflammation and promote cell proliferation by producing growth factors and through initiation of the arginase pathway, neoangiogenesis and tissue repair (Mantovani, 2007). In the presence of malignancy, a higher than normal proportion of macrophages belongs to this prototypic M2 population and this appears to alter the balance of immune responses (Sánchez-Torres, 2001). In fact, while in healthy individuals M2 monocytes comprise only 10% of the total monocytic population, this proportion in tumor patients may be as much as 40% higher (Sánchez-Torres, 2001). In malignancy, natural killer T cells (NKT) may have a protective effect by producing interferon-gamma, which activates both M1 and DC1 dendritic cells. These latter cells secrete IL-12, thereby increasing anti-tumor activity. On the other hand, NKT-2 cells inhibit tumor immunity (Terabe and Berzofsky, 2008). These opposing effects of different NKT cell lines provide a further example of the complexity of immune imbalance in cancer patients.

While numerous studies employing different immunological techniques failed to provide evidence for a major role of T-cells in general in anti-tumor immunity (Nagtegaal et al., 2001), other studies specifically focusing on effector cells had more positive results. In particular, NK cells were identified as key players in eliminating tumor cells. Additionally, the administration of cytokines inducing natural killer cell response in combination with chemotherapy had additional benefits, including slowing tumor progression and improving survival (Wang et al., 2013). One must also remember that an important mechanism by which malignancy induces immunosuppression is through the induction of Treg cell proliferation as well as proliferation of other cell lines such as type-2 dendritic cells, which inhibit NK cell activity by decrease production of IL-12 (Mantovani, 2007).

Effect of various types of oncological treatments and interventions on the tumor-induced immune imbalance

Cytostatic chemotherapy is widely used in various types of malignancy. However, with this therapy, complete remission is sometimes difficult to achieve, depending on the type of cancer. The effect of cytostatic drugs is not confined to malignant cells; they affect healthy cells among them immunocompetent cells. It seems therefore important to assess the influence of routine chemotherapy on tumor-related immune dysfunction. As far as mechanisms, many of the cytotoxic drugs can reduce the NK cell population, decrease IL-2 production and diminish antibody dependent cell-mediated cytotoxic (ADCC) activity. The suppression of the immune response reaches its peak in 3-4 weeks, with potential partial restoration of immune activity after 5 to 6 weeks (Saijo et al., 1982; Rafique et al., 1997; Kikuchi et al., 1997).

The immunosuppressive effect of surgery is widely recognized. Postoperative activity of NK cells is significantly lower compared to preoperative values, and this effect lingers postoperatively for a long period of time (Bruns et al., 1996; Vallejo et al., 2003).

The imbalance of the immune response in cancer patients is also associated with common tumor-related symptoms including fatigue and pain. When either of these symptoms are present, decreased activity of phagocytes and NK cells are often seen (Welden et al., 2009; Miller et al., 2008). This in turn leads to an alteration in the balance between type-1 and type-2 responses with elevated activity of regulatory T cells (Liu et al., 2009). This raises the possibility that analgesic treatments may be beneficial in these patients. Opioids would be the most logical candidates, except for the fact that they may have a more direct effect on the immune system on their own. When healthy volunteers were exposed to a morphine drip for a 36 h time period, this was associated with a suppression of both NK and phagocytic functions, confirming a direct effect of morphine on immunity (Yeager et al., 1995; Clark et al., 2007).

Considerations for establishing a clinical strategy to improve anti-tumor cellular immune response through immunomodulatory treatments

Although it is well established that cellular immunity is suppressed in malignancy, an effect further worsened by chemotherapy, this fact is not routinely considered in current clinical practice and did not inspire sufficient clinical research. This has led to the current state of affairs where insufficient experience and overall lack of understanding of the particular mechanisms prevent us

from investing in studies to establish the worth of immunomodulatory treatment. We argue that if a clinical tool was available to test the degree and specific pattern of immunocompromise in cancer patients, this could open the way for an individualized immunomodulatory treatment of immune imbalance in these patients.

One should also keep in mind the different mechanisms through which the two main types of cellular immune responses affect tumor growth. While in cancer patients, type-1 cells are activated inducing immune reactions that result in the eradication of tumor cells, eventually type-2 cells also become involved promoting tumor growth. If one was to devise an immunomodulatory therapy with the objective of boosting cellular immunity against malignancy, one should know exactly where an individual patient stands in the evolution of immune imbalance (Yeager et al., 1995).

PROMISING PRECLINICAL AND CLINICAL RESULTS AND PERSPECTIVES OF IMMUNOMODULATORY TREATMENTS

Restoring immune imbalance-what do we know from clinical studies?

More than twenty years ago after the discovery of interleukin (IL)-2, Lymphokine Activated Killer cell (LAK) therapy was introduced, which seemed to achieve surprisingly rapid tumor remissions. It was soon realized that the activation of NK cells played the primary role in these successful treatments. In a recent paper, Levy and Roberti discussed the role of natural killer cells in human cancer (Levy et al., 2011; Roberti et al., 2012). As is well known, NK cells are some of the most important effector and regulatory cell populations of the innate immune system. As a result of this recognition, immunological research was for a long while primarily focused on NK cells in anti-tumor defense. Unfortunately, IL-2 is a highly toxic cytokine and its use produced a number of undesired side effects which considerably lowered enthusiasm for any further development of LAK therapy. In addition, it was also established that the activation of NK cells is not always accompanied by enhanced tumor cell killing- this same phenomenon was also observed during interferone therapy. Today, we can safely conclude that the role of NK cells in the rather complex network of innate immune system was overemphasized and the complexities of immune imbalance were poorly understood. It is small wonder that effective treatments could not be devised with such spotty understanding of mechanisms.

It is well known that when activated, NK and Th1 cells are important interferone-gamma producers and by this effect they can induce enhanced expression of MHC-I antigens on the cell membrane of every nucleated cell.

Immunomodulatory treatments can enhance this effect. However, though increased MHC-I expression can be favorable for T cell-mediated adoptive immune reactions, it can also induce unfavorable mechanisms since MHC-I antigens on tumor cells can operate as Killing Inhibitor Receptors (KIR). Increased expression of KIR receptors on the surface of tumor cells may result in decreased efficacy of natural killer cells on these tumor cell lines. One is well advised to bear in mind this phenomenon, particularly when treating malignancy of a more advanced stage. In this circumstance, the relative role of the effector cells belonging to the innate immune system takes over the importance of adoptive responses (Nagtegaal et al., 2001; Clark et al., 2007) compromising efficacy of such therapies at this stage. In one study, for instance, when the relative significance between specific adoptive immune responses and non-specific reactions of innate immunity were compared and their relative contribution to prognosis analyzed, results revealed that although there was a significant anti-tumor response by the adaptive immune response as reflected by increased T cells activation, patient survival and tumor recurrence was affected more by non-specific responses by the innate immune system (Nagtegaal et al., 2001). However, persistent activation of effectors of the innate immune system such as NK, NKT and $\gamma\delta$ T cells together with Th1 cells can also upregulate KIR receptors on tumor cells by enhanced production of interferone-gamma. Consequently, the cellular cascade mechanisms against tumor cells will only be effective for a relatively short period of time and immunomodulators treatments need to be given periodically with therapy-free intervals of at least 72 h inserted between treatments. This was previously demonstrated in an animal model (Hajtó et al., 1998). To summarize, we need to devise our immune therapy in such a way that while we induce effector mechanisms by innate immunity, we also need to achieve periodic down-regulation of MHC-I expression (Garrido et al., 1993; Lotfi et al., 2009). Subsequently, the clinical benefit of the down-regulation of MHC antigens by fermented wheat germ extract will be detailed.

Can we enhance the effectiveness of monoclonal antibodies by immunomodulators? Interaction of cetuximab with NK cells

As published previously and discussed subsequently, a combination of plant immunomodulators with Avastin (VEGFR inhibitor) induced a complete remission of hepatic metastases (Hajtó and Kirsch, 2013). As part of a complex regimen of oncotherapy, monoclonal antibodies (mAbs) have a central role in individualized cancer treatment. Recently, several studies undertook to further our understanding on monoclonal antibodies as they activate and/or enhance tumor-specific immune responses.

It appears that these antibodies act either by interrupting intrinsic signal transduction cascades inside tumor cells, or by specifically delivering toxins to malignant cells as they block the tumor-stroma interaction (Vacchelli et al., 2013). Even though most studies focus on these aforementioned specified mechanisms by mAbs, monoclonal antibodies also have immuno-modulatory properties and they can activate the secretion of several substances crucial in the development of the immune response (Levy et al., 2011). These functions are less studied and remain poorly understood.

Cetuximab, a monoclonal antibody, binds to the extracellular domain of EGFR, an antigen overexpressed in many different types of human cancers (Bou-Assaly and Mukherji, 2010). These types notably include head and neck and colorectal cancer. This process prevents EGFR from binding its endogenous ligand, blocking the receptor-dependent transduction pathway. This results in an anti-tumor effect due to a number of mechanisms including cell-cycle arrest, induction of apoptosis, inhibition of angiogenesis, inhibition of metastasis, internalization and downregulation of EGFR and increased sensitivity to radiotherapy and chemotherapy (Hidvégi et al., 1999). Levy et al. (2009) and Correale et al. (2010) showed that NK cells produce cetuximab-mediated ADCC in metastatic colorectal cancer (mCRC). They also demonstrated that this activity is not affected by the mutational status of the molecule K-RAS. As they correctly state in their paper, this effect confirms previous observations that NK cells recognize the surface-bound Abs and are able to kill tumor cells independently from EGFR pathway activation. However, the failure of cetuximab-mediated ADCC to induce clinical remissions in mCRC patients with K-RAS mutations remains largely unexplained. One of the possible factors involved could be the low proportion of NK cells infiltrating CRCs and the low functional capacity of these cells in cancer patients (Levy et al., 2009; Pagès et al., 2009; Wulff et al., 2009). If it was possible to enhance the activity of NK cells, the efficacy of cetuximab treatment as well as treatment with other mAbs (e.g. bevacizumab) could be improved. Furthermore, passive immunizations such as the ones affected by mAbs can also suppress innate cellular immunity by worsening cancer-related dysfunction.

PROMISING PRECLINICAL AND CLINICAL RESULTS WITH PLANT IMMUNOMODULATORS

Early results with immunomodulation therapy and clinical studies

The immunomodulatory effect of mistletoe therapy, one of the better-studied forms of immunomodulation therapy, is based on lectin-carbohydrate interaction on cell membrane surface of several immunocompetent cells of

the innate immune system (Hajtó et al., 1989; Hostanska, 1996-97; Hajtó et al., 1990; Hajtó et al., 1998). These cells including granulocytes, macrophages, dendritic cells and natural killer (NK) cells are activated by infection and by tumor cells if their pattern recognition receptors (PRR) are bound by pathogen-associated molecular pattern (PAMP) ligands. There is evidence accumulating that mistletoe lectins (ML) may also act as PAMP ligands. MLs are able to bind PRR molecules on phagocytes; this binding shows some similarity with interactions between Toll-like receptors and PAMP ligands of microorganisms. Mistletoe lectins, functioning as ligand for pattern recognition receptors of the innate immune system, are docked to ganglioside molecules (CD75) of certain natural immune cells. Through this interaction, MLs are capable of partially restoring the immune imbalance in tumor patients (Hajtó et al., 2011; Müthing et al., 2004). The active (that is, carbohydrate-bound) lectin content of commercially available Iscador^R M preparation was measured by an optimized form of ELLA technique (Hajtó et al., 2007).

Research with tumor models using *nude mice* xenotransplanted with human leiomyosarcoma as well as *interleukin-12-deficient C57BL6 mice* show that without modulating cellular immune responses, the cytostatic effect of MLs alone (such as their ML-mediated inhibition of cell cycles in S phase) would not in itself yield an anti-tumor effect (Duong van Huyen et al., 2006; Elluru et al., 2007; Hajtó et al., 1990). Clinical experience and several case reports tend to confirm these early results from basic research (Hajtó et al., 1991; Kirsch, 2007; Kirsch and Hajtó, 2011; Hajtó and Kirsch, 2013).

In a previous case report, the clinical progress of six sarcoma patients showed remissions of tumor symptoms (Kirsch and Hajtó, 2011). In a subsequent clinical study, sarcoma patients were treated with a combination therapy including mistletoe extract. Dose was standardized for active (that is, sugar-bound) lectin content. Dose-response relationships were established and found to be bell-shaped. Finally, it was decided to give a dose of 0.5 to 1.0 ng/kg ML subcutaneously twice a week. Time to remission appeared to be dependent on the exact composition of the combination therapy. As shown in Figure 1, standardized mistletoe extract therapy alone resulted in a partial (near-complete) remission after 15 months (Figure 1A), while its combination with epirubicin achieved complete remission in as little as three months (Figure 1/B). This indicates that a combination of immune therapy and cytostatic drugs may be of additional benefit compared to a monotherapy with either substance.

Improving quality of life with immunomodulatory treatment

In the last decades, special attention has been focused on the role of immune imbalance on symptoms influencing

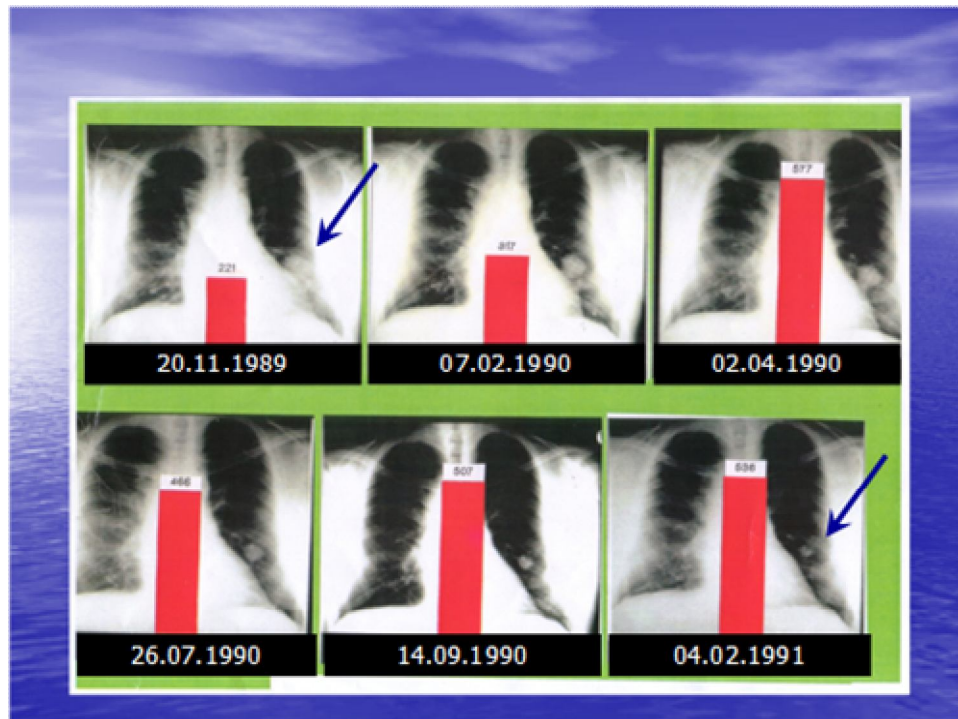


Figure 1A. Effect of immunomodulatory treatment in a patient with sarcoma not receiving standard oncological therapy-an example of a slow response. Chest radiograms of a patient with liposarcoma showing lung metastasis; from November 1989 the patient was treated with mistletoe extract with standard lectin content as monotherapy, that is, without other oncotherapeutic modalities. The dates of X-rays were: 1) Nov 20th 1989; 2) Febr 7th 1990; 3.) April 2th 1990; 4) July 26th 1990; 5) Sept 14th 1990; 6) February 4th 1991. As shown with arrows, within 15 months after initiation of treatment a partial (near-complete) remission was observed. The red columns illustrate the increasing frequency of circulating NK cells in peripheral blood.

quality of life. Impaired quality of life (QoL) appears to correlate with increased morbidity and mortality. Moreover, it can adversely affect treatment adherence (Miller et al., 2008; Reiche et al., 2005). As stated above, behavioral symptoms in cancer patients are also associated with abnormal immune response. Specifically, decreased activity of cellular immune response by the innate immune system with elevated activity of regulatory T cells appears to be a typical pattern (Liu et al., 2009). Most commonly, this pattern is observed in association with fatigue, depression, pain and cognitive dysfunction (Miller et al., 2008). Due to this association, there is growing interest in studying the potential influence of immunomodulatory treatment on quality of life-related symptoms.

In one study, QoL of 27 patients suffering from various advanced stage malignant tumors was assessed using SF-36 questionnaires (Takahara and Sano, 2004; Ware and Snow, 1993; Ware et al., 1998; Akakura et al., 2011). All patients were treated with mistletoe extract with standard lectin activity given in immunologically effective doses twice a week for two years. To monitor their QoL

during this period, SF-36 questionnaires were regularly filled out at four-month intervals. SF-36 scores were compared to untreated pair-matched controls. The score values were evaluated at 0, 4, 8, 12, 16, 20 and 24 months following initiation of treatment. As shown in Figure 2, significant differences in score values between patients and controls were found after 12, 16, 20 and 24 months. Among tumor-related symptoms, particularly great benefit was obtained in fatigue and pain. The authors concluded that the standardized plant immunomodulators can be helpful in the improvement of QoL of tumor patients.

Benefits obtained from combination of plant immunomodulators

Similar to mistletoe extract, modified arabinoxylan preparation obtained from rice bran (MGN-3/BioBran[®]) was also found to stimulate type-1 cells in the innate immune system; more specifically, it increased NK cell activity both *in vivo* and *in vitro* (Ghoneum, 1998) and

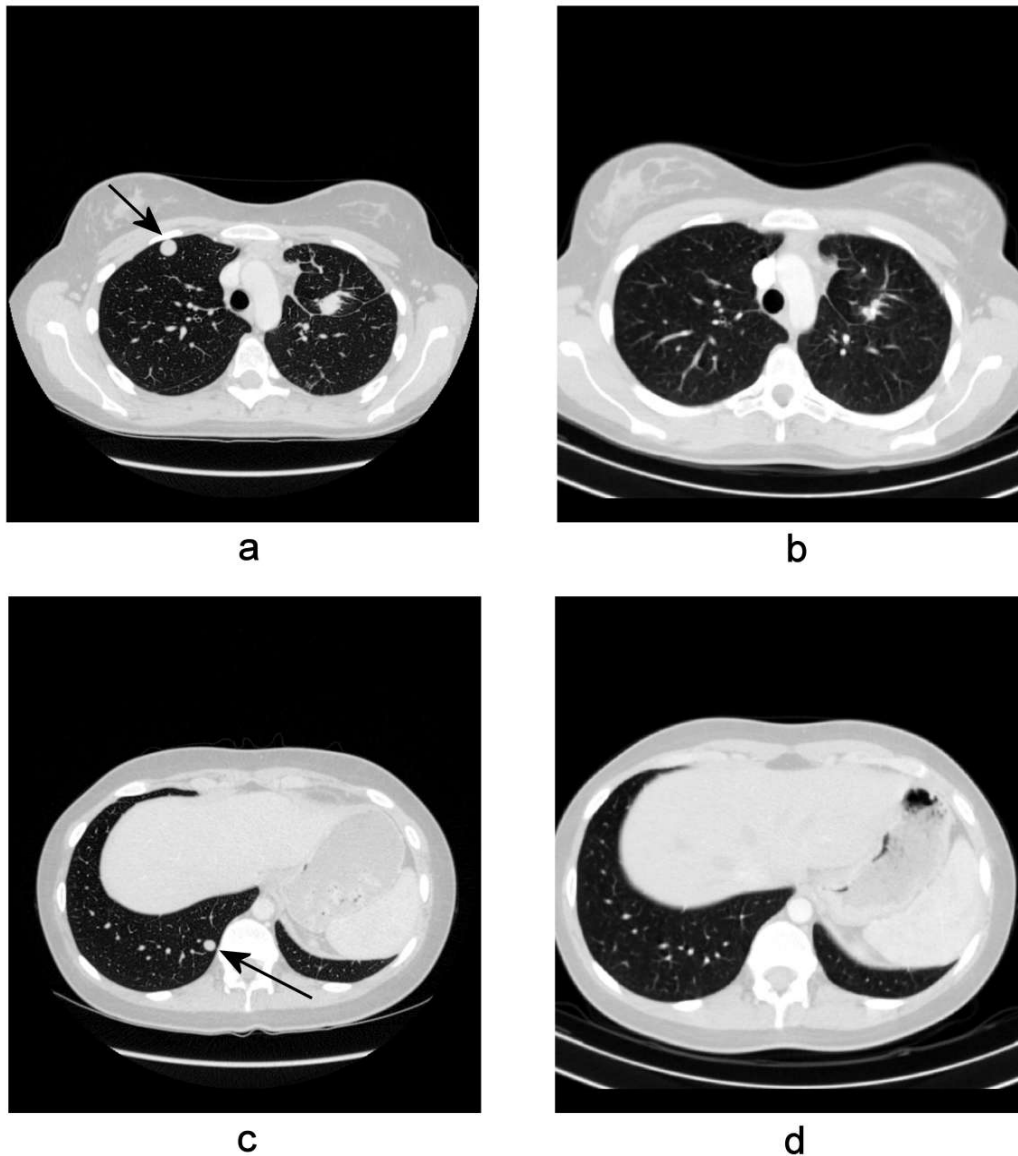


Figure 1B. Fast response obtained with immunomodulatory treatment added on chemotherapy in a sarcoma patient. CT images showing lung metastases in a patient with stroma sarcoma. As shown with arrows, in segment III (right) 14 mm [a] and in segment X (right) 9 mm [c] metastases were observed in November 2009. After 2 cycles of 90 mg/m² Epirubicin in combination with ME and MGN-3 therapy, complete remissions were achieved [b and d, respectively] by January 2010. As demonstrated on follow up CT images from April 2010 and January 2011, no recurrence occurred during this time period.

increased phagocytic function by macrophages (Ghoneum and Matsuura, 2004). Given as combined therapy, mistletoe lectins (in mistletoe extract) and modified arabinoside appears to have an additive effect (unpublished data), which is not surprising because of the stimulatory effect of arabinoside on various plant lectin (Phytohemagglutinin, Concanavalin-A and Pokeweed)-induced mitogen responses as described previously (Ghoneum, 1998). In addition, as shown in Table 1, case

reports and clinical trials have been also shown that the modified arabinoside - induced immunomodulation results in an anti tumor effect (Takahara and Sano, 2004; Bang et al., 2010; Kaketani, 2004; Kawai, 2004).

A third substance used in the previous presented immunomodulation therapy is wheat germ extract (WGE/Avemar[®]) containing 2, 6-DMBQ in 0.4 mg/g concentration as dry preparation (Hidvégi et al., 1999). Based on the idea of the Nobel laureate Albert Szent-

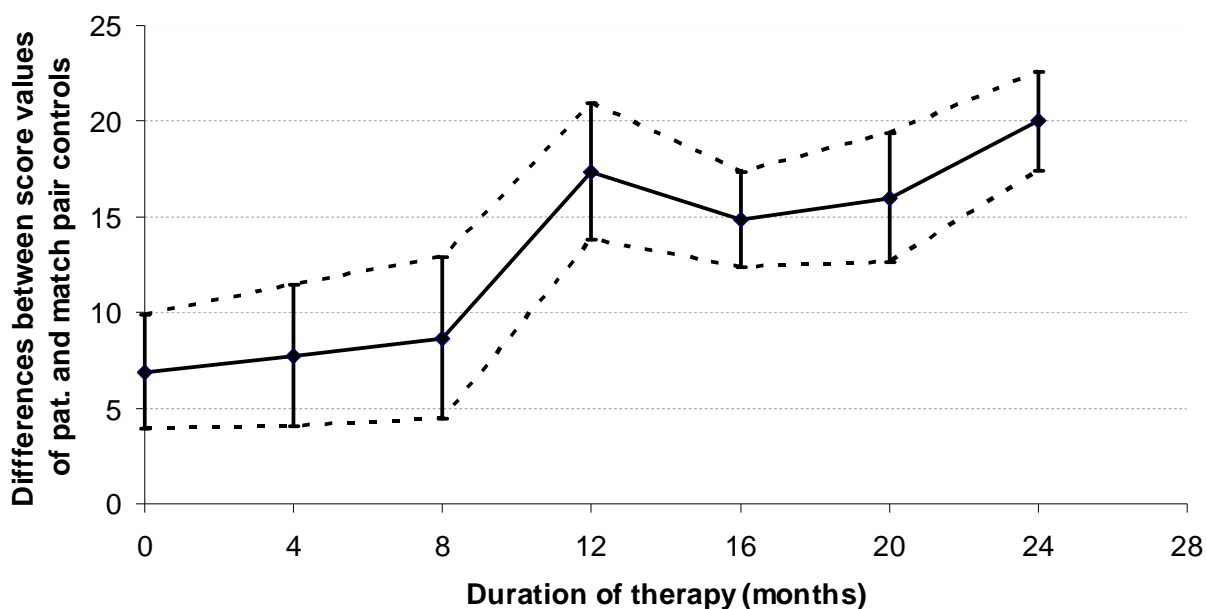


Figure 2. Effect of immunomodulatory treatment on quality of life scores. Changes in quality of life observed in 27 case reports on patients suffering from a variety of malignancies in advanced stages. Patients were treated with mistletoe extracts standardized for lectin activity and given in immunologically effective doses (0.5 and 1.0 ng ML/kg) twice a week for two years. The score values of SF-36 questionnaires were evaluated at four-month intervals and compared to matched controls. Average differences (+/-SEM) are shown; at 12, 16, 20 and 24 months significant elevations in QoL were found: 17.36 (+/-3.55), $p < 0.01$; 14.85 (+/-2.51), $p < 0.02$; 16 (+/-3.34), $p < 0.05$; 20 (+/-2.6), $p < 0.01$, respectively. The average SF-36 score values of patients rose from 129 +/- 3 to 139 +/- 2.6 in the treatment group; they remained constant in the control group (123 +/- 4 at month 0 vs. 122 +/- 6 at month 24).

Table 1. List of plant immunomodulators discussed in this paper.

Name of plant preparation	Active ingredient	Status in clinical trials which can support an effectiveness against cancer
Mistletoe Extract (ME) [Iscador ^R –M spec 5 mg]	Mistletoe Lectins (ML)	Pilot Clinical Study: Hajt6 et al., 1991; Case reports: Kirsch, 2007; Kirsch and Hajt6, 2011; Hajt6 and Kirsch, 2013.
Rice Bran Preparation [BioBran ^R /MGN-3]	Modified Arabinoxylan	Pilot Clinical Study: Takahara and Sano, 2004; Randomized Clinical Trial: Bang et al., 2010; Case Reports: Kaketani, 2004; Kawai, 2004
Wheat Germ Extract [AveMar ^R]	2.6-dimethoxy-p-benzoquinone	Phase-II-Clinical Trial: Jakab et al., 2000. Case Report: Hajt6 and Kirsch, 2013.

Gy6rgyi, WGE was developed by a Hungarian scientist, Mate Hidvegi in the last decade of the 20th century. Since then both *in vitro* and *in vivo* studies confirmed a significant anti-metastatic effect by WGE (Szent-Gy6rgyi, 1982; Jakab et al., 2000; Boros et al., 2005). The combination of WGE with NK stimulatory substances, such as mistletoe extract and arabinoxylan is promising since WGE also induces a downregulation of major

histocompatibility complex (MHC) class I proteins (Fajka-Boja et al., 2002) and thus may have an additive effect to those of other immunomodulators. As described earlier, this downregulation of MHC class I proteins reduce the effect of killing inhibitor receptors (KIR) resulting in enhanced killing of tumor targets by NK cells. Clinical investigations with WGE alone also revealed an inhibitory effect on hepatic metastases of patients with colon

Table 2. Proposed doses and application schemas for plant immunomodulators discussed in this paper.

	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
ML in standardized ME	0.5-1.0 ng/kg s. c.			0.5-1.0 ng/kg s.c.			
MGN-3 standardized for Arabinoxylan	12-45 mg/kg p.o.			12-45 mg/kg p.o.			
WGE standardized for 2,6 dimethoxy p-benzoquinon	50-80 mg/kg p.o.l	50-80 mg/kg p.o.		50-80 mg/kg p.o.	50-80 mg/kg p.o.		

Abbreviations: ML = mistletoe lectin; ME = mistletoe extract; MGN-3/ BioBran^R = fermented heteropolysaccharide rice bran preparation; WGE = wheat germ extract / Avemar^R.

cancer (Jakab et al., 2000).

Other biological properties of these plant preparations may also play a role in their beneficial effects, such as stimulation of apoptosis (Hajtó et al., 1990; Fajka-Baja et al., 2002; Hajtó et al., 2005; Boros et al., 2005) or inhibition of cell cycles in S phase (Hajtó et al., 1990; Fajka-Baja et al., 2002; Boros et al., 2005). 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 (Hajtó et al., 1990; Duong van Huyen et al., 2006).

Standardized plant extracts described above have a great advantage; they do not 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 site of injection after 8 to 10 h) was observed between 0.9 and 43% (Bock, 2004). BioBran^R/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 (Tsunekawa, 2004). WGE has been put on the market as a non-toxic dietary supplement. Toxicological studies with high doses of WGA (3 g/kg) did not show any deviation from the controls (Fajka-Boja et al., 2002).

Recent case reports and case series on patients with hepatic metastases also confirm these putative additive effects of different immunomodulators. One such case series by Hajtó and Kirsch (2013) used a combination treatment with mistletoe extract standardized for active lectin content in doses 0.5 and 1.0 ng/ml/kg twice a week subcutaneously; 12 to 45 mg/kg MGN-3 / Biobran^R with standard arabinoxylan content given twice a week; and 50 to 80 mg/kg WGE/Avemar with standard 2, 6-dimethoxy-p-benzoquinone content given four times a week. A schema for the proposed combination therapy with the three main immunomodulators described above

is demonstrated in Table 2. In this case series, all seven patients achieved complete or near-complete remission of hepatic metastases (Hajtó and Kirsch, 2013). It appears then that in patients with hepatic metastases a combination treatment with immunomodulators can be useful adjunctive therapy to more conventional interventions such as surgery, hormone treatments or chemotherapy. The combination of these plant immunomodulators (ME, MGN-3 and WGE) with conventional oncological treatments can render possible complete remissions which are rarely attainable by oncological therapies only. As known, the patients with hepatic metastases after chemotherapy can rarely reach a greater reduction than 50%, and the response is short. It can also occur that a plant immunomodulator alone induces a tumor remission, as it is demonstrated in Figure 1A. Sarcoma patients were found often sensitive to immunomodulatory treatment (Kirsch and Hajtó, 2011) and therefore the question arises, whether various types of tumors can react to this immunomodulatory treatment in different degree? In spite of the possibility that various tumor cells can exhibit different sensitivity to immune responses, it is not easy to judge since a great tumor burden is always less susceptible for therapeutic influence.

As presented in a previous paper (Hajtó and Kirsch, 2013), a case report showed an important and rapid remission of hepatic metastases 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. In addition, two case reports showed a remission after a combined therapy of hormones (anti-estrogens) and immunomodulators. As it 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. In order to further substantiate these claims, more rigorous research is urgently needed.

CONCLUSION

We propose that at the present time enough research data is available to warrant more attention by clinical practitioners to the tumor-induced imbalance of the innate immune system. In fact, the restoration of adequate anti-tumor immune response should be an important clinical goal. In order to achieve this aim, immunomodulators consisting of plant extracts with standard doses based on their active ingredient should be considered as adjunctive therapy in addition to standard treatments. Such combination treatments may be particularly effective in cases where treatment with epidermal growth factor receptor monoclonal antibody (such as cetuximab) is given. Immunomodulators can improve the quality of life of tumor patients-this improved life quality often translates into better outcomes after standard treatments with surgery, chemotherapy or radiotherapy. Further clinical trials are necessary to clarify the beneficial effect of combination treatments with currently available immunomodulatory substances.

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