



Stabilization of Chronic Lymphatic Leukemia with *Amanita phalloides*: Effect of Additional *Chelidonium majus*. Case Report

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

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Case Study

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ABSTRACT

Objectives: *Amanita phalloides* contains amanitin, inhibiting RNA polymerase II. Partial inhibition with amanitin influences tumor cell - but not normal cell - activity. A patient with diagnosed B-cell chronic lymphatic leukemia was treated successfully for eight years with *Amanita phalloides*. However, the necessary dose for stabilization of the disease increased during this time. In addition thrombocyte levels decreased, indicating bone marrow affection. Therefore additional regimen was necessary.

Methods: *Chelidonium majus* contains alkaloids with cytostatic and cytotoxic potential. In addition to Amanita, Chelidonium was applied.

Results: During treatment with Amanita and Chelidonium, leukocyte levels and lactate-dehydrogenase levels were roughly unaffected, meaning there is no strong effect on tumor growth of cells, and no observable cell destruction. Anyhow, thrombocyte levels increased after the Chelidonium treatment, indicating an effect in the bone marrow.

Conclusion: *Chelidonium majus* can be useful during Amanita therapy as a pulse to regenerate bone marrow affection.

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1. INTRODUCTION

In a genetic attempt with tumor-forming *Drosophila melanogaster*, four classes of genes involved in tumor formation have been distinguished: Proliferative genes break the cell cycle control by allowing replication immediately after mitosis. One single proliferative mutation is sufficient for tumor formation [1]. Mutations in oncogenes and tumor-suppressor genes are secondary events and add by destabilization of the differentiation pattern of the cells. The central possible targets for therapeutic intervention were identified: Switch genes. Functionally, these are *HOX* genes and all code for RNA polymerase II (RNAP) transcription factors. Some *HOX* genes are overexpressed in human tumor cells. Due to this, the event that leads to tumor cell growth, should lead to high activity of RNAP. In somatic cells of adults, RNAP is expected to be less active. Partial inhibition of this enzyme consequently causes inhibition of tumor cell activity, without severe effects on somatic cells. The drug in the extract of *Amanita phalloides*, amanitin, blocks RNAP in all cells. Inhibition of about 50% of this molecule has no effect on normal body cells, but breaks the activity of tumor cells. The immune system recognizes and digests the latter. Amanita treatment already showed good results in stabilization of a number of tumor cases, including Chronic Lymphatic Leukemia (CLL) [2].

CLL is the most frequently occurring leukemia in the Western hemisphere, with an incidence of 4 in 100,000. Patients with CLL are managed according to their individual risk with a watch-and-wait strategy, until cell count is above 200,000 leukocytes per μl blood [3]. This leukemia is understood to originate from tumor growth within the hematopoietic system. However, in a patient with CLL and an additional *Borrelia* infection, the CLL disappeared in conjunction with the borreliosis, indicating that *Borrelia* can induce the clinical picture of a CLL [4].

One of the complications in leukemia, finally inducing the anemia, concerns the bone marrow. Neoplastic cells can gain room there, and the stem cells of the white and red systems are displaced. This can lead to a deprivation of any kind of blood cell. Most frequent is a deprivation first in thrombocytes, followed by deprivation of erythrocytes, finally causing the anemia.

In Europe and China, *Chelidonium majus* – containing orange latex - is used since long in phytotherapy. Extractions of the plant or isolated components are used with a large variety of therapeutic impacts. Protection of the liver is an outstanding use [5]. Many therapeutic effects are meanwhile verified by biochemical experiments. *Chelidonium majus* is used since Hahnemann as homoeopathic drug for liver protection that stimulates choler excretion. It is applied against asthmatic cough and is related to the kidney. Homoeopathic dilutions were successfully applied to mice with induced liver carcinoma, or against malaria [5,6].

The plant contains up to 1.5% alkaloids. Chelidonine, coptisine, chelerythrine and sanguarine have cytotoxic potential [7-10]. Chelidonine and sanguarine alone can induce apoptosis of cells. Chelidonine arrests cells at the end of the G2-phase, whereas sanguarine destroys the DNA [11]. Chelidonine induces thereby the p53 cascade [12]. Molecular induction of Caspase 3 and Caspase 8 occurs. Caspases are involved in apoptosis induction. Reduction of the activity of ABC transport proteins is described. Those transport proteins limit the uptake of chemicals into the cell, and therefore lead to chemotherapy resistance [13]. Tumor cells react to extractions of *Chelidonium majus* and change their chemosensitivity. With 50 μM chelidonine during 48 hours, resistance to chemotherapeutics of cells in culture can be eliminated. In tumor cells, telomerase hTERT is active. Chelidonine inhibits this enzyme and induces herewith aging of cells. It breaks the activity of cells. A dose of 2 μM already suffices to obtain a maximum inhibition of cell growth of 50%. Higher doses do not lead to higher inhibition rates [14]. GABAA receptor is in discussion to play a role in metastasizing tumor cells [15]. *Chelidonium majus* extracts interact with GABAA receptor. This is due to a mixture action of several alkaloids [16].

The latex contains as well nucleases and other enzymes that react on apoptosis induction of the cell. [17] Chelidonat has antiphlogistic potential and is in discussion to modulate the immune system. The latex contains as well anti-viral, anti-bacterial and anti-fungal substances.

Therapy with *Chelidonium majus* can lead to acute hepatitis [18-19]. This form of hepatitis is reversible, breaking the treatment leads to recovery.

Cytostatic and cytotoxic effects break and eliminate growing cells. Non growing cells are not affected. Here a therapy attempt of *Chelidonium majus* together with *Amanita phalloides* in a tumor patient is presented.

2. PATIENT AND METHODS

The patient was born in 1957 and works in the field service. B-CLL was first diagnosed in 2005, appearing to be slowly progressive. His body weight was 77 kg and remained constant throughout the therapy. No additional disease was diagnosed initially. The initial exponential growth of leukocytes revealed a period of 21 months for duplication. A hypogammaglobulinaemia was diagnosed (Table 1). The bone marrow showed a 70% infiltration of small mature lymphatic cells into the hematopoietic system. CD38 expression of the cells was negative, normal karyotype was diagnosed. No deletion of 11q or 17p occurred. No aberration on chromosome 12 or 13 were detected. Amanita therapy started at the end of 2007 at a cell count of 126 (x1000) leukocytes per μL blood (LEU). This leukocyte level is too low for conventional treatment. The patient decided to undertake a therapy attempt with Amanita until a level of 200 LEU was achieved or until a potential liver cell damage appeared. In parallel, all prearrangements for conventional therapy occurred. Patient's history did not indicate any specific risk for tumor formation. He subsists on vegetarian food and often suffers from low iron levels. He shows no symptoms of leukemia, no lymph node swelling, and does not have frequent infections. The erythrocyte cell count is at a low level within the normal range. No other tumor-specific therapy than the indicated ones were applied. Adjuvant uptake of additional essential fatty acids (to enhance fluidity of cell membranes and to provide raw material for prostaglandins, i.e., immune cell hormones), iron (orally), and zinc (cutaneous) was given. Noxes (i.e., long airplane flights or radiation) were avoided as far as possible.

Amanita therapy started with *Amanita phalloides* (zert. Riede) D2 [Herbamed AG, CH] in January 2008 [2]. With 100 ml of this drug, about 50% of all RNAP molecules in all cells are inhibited. Degradation of the drug cannot be named. With different doses, until today, the patient is stabilized to a B-cell count between 100 - 200 LEU. The initial phase (Fig. 1) showed strong reaction of the tumor cells upon the therapy. After the application of about 100 ml of the drug

in March 2008, leukocyte levels decreased dramatically in April 2008. This is accompanied with an increase of lactate-dehydrogenase (LDH). This enzyme is present in all cells, occurrence of higher levels indicate cellular destruction. Therefore, it can be concluded, that leukocytes vanish through cellular lysis. During this period the patient suffered from severe inflammation symptoms: He had fever, lymph nodes showed up. Therefore it can be concluded, that the immune system is involved and digests the tumor cells. The therapy was interrupted and within two weeks, leukocyte level was back to higher levels. This elevation is too fast for tumor growth of cells and is interpreted as originating from migration of leukocytes from the periphery. In addition to lymph node involvement, the patient suffers from swollen fingers, indicating an involvement of the kidney. All symptoms vanished after a week.

Start Amanita phalloides

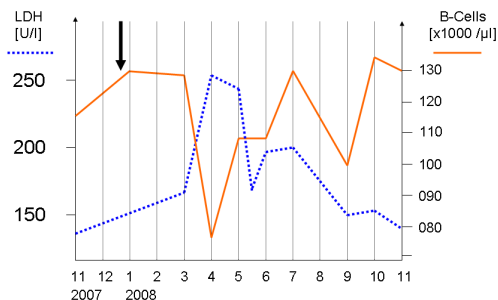


Fig. 1. Amanita therapy

Shown is the beginning stage of the Amanita therapy in 2008. The red line indicates leukocyte level in the blood, the blue dotted line shows LDH level.

Arrow: Start with Amanita phalloides (zert. Riede) D2

For stabilization, end of 2008 the average monthly dose was at 10- 15 ml *Amanita phalloides* D2. End of 2010 already 35 ml per month were necessary. Today, roughly 50 ml per month are applied. So, continuous higher doses are necessary to avoid activation of the tumor cells.

Chelidonium majus D1 [herbamed AG, CH] usually is applied in 2 x 10 drops per day. This dosage correlates with the uptake of 100 ml in about two months, containing about 150 mg chelidonine. After about a week, a level of 750 $\mu\text{g}/\text{kg}$ body weight is reached, correlating with the therapeutic dose of 2 μM , the dose with the maximal effect of cell growth inhibition in vitro [14]. Degradation rate of the drug cannot be named.

Table 1. Monitoring parameters

Parameter	Oct-05	Jan-08	Sep-12	Jun-13	Jun-14	Jun-15	Standard
Erythrocytes	4.6	4.48	4.11	4.19	4.22	3.96	3,5-5,5 ~12/l
Hematocrit	42	41.7	39.1	40.1	40.9	39.2	35,0-55,0%
Hemoglobin	14.7	13.2	13.3	13.4	14.1	12.6	11,5-16,5 g/dl
Mean corpuscular Volume	92	93	95.2	95.8	96.9	98.8	75,0-100,0 fl
Mean corpuscular Hemoglobin	n.a.	29.5	32.5	32.0	33.5	31.8	25,0-35,0 pg
Mean corpuscular/Cellular hemoglobin concentration	n.a.	31.7	34.1	33.4	34.5	32.1	31,0-38,0 g/l
Granulocytes	4.4	5.6	3.2	3	2.5	3.5	35,0-80,0%
Lymphocytes	93.3	88	95	95.2	96.1	94.2	15,0-50,0%
Monocytes	1.5	6.6	1.8	1.8	1.4	2.3	2,0-15,0%
Sodium	141	148	138	144	143	146	137-147 mmol/l
Potassium	4.7	4.4	4.1	4.3	4.8	4.6	3,8-5,3 mmol/l
Calcium	2.4	n.a.	2.1	2.4	2.3	2.2	2,1-2,6 mmol/l
Chloride	104	n.a.	n.a.	104	103	104	98-106 mmol/l
Phosphate	n.a.	n.a.	n.a.	3.0	3.4	3.1	2,7-4,5 mg/dl
Glucose	n.a.	58	106	73	78	75	70-110 mg/dl
Uric Acid	5.1	5.9	5.7	6.0	6.6	6.7	<7 mg/dl
Urea	38	n.a.	n.a.	34	38	36	10-50 mg/dl
Bilirubin	0.8	0.8	0.4	0.6	0.7	0.6	<1,1 mg/dl
Lipase	34	35	33	29	31	32	13-60 U/l
GGT	17	20	15	18	18	18	<64 U/l
GPT	21	18	21	16	20	22	10-50 U/l
GOT	17	19	23	20	17	23	10-50 U/l
Cholinesterase	n.a.	8.1	6.8	7.4	7.4	6.8	5,3-12,9 kU/l
Glutamatdehydrogenase	n.a.	n.a.	<1,0	<1,0	<1,0	1.0	<7 U/l
creatinin	1.22	1.2	1.3	1.1	1.1	1.2	<1,2 mg/dl
Alkaline phosphatase	84	100	106	107	109	109	40-129 U/l
Creatinin kinase	n.a.	n.a.	n.a.	73	120	127	<190 U/l
LDH	142	150	149	180	184	167	135-270 U/l
Protein	6.5	6.9	5.8	6	6.1	5.8	6,5-8,5 g/dl
Albumin	69.2	68	71.2	71.5	70.6	71.3	55,8-66,1%
alpha1 globulin	3.6	4.3	4.2	4.1	4.2	4.2	2,9-4,9%
alpha2 globulin	9.3	10.2	9.3	9.7	9.7	9.9	7,1-11,8%
beta1 globulin	5.1	5.2	5.6	5.1	5.8	5.6	4,7-7,2%
beta2 globulin	3.8	3.6	2.8	3.0	3.3	3.3	3,2-6,5%
gamma globulin	9	8.7	6.9	6.6	6.4	5.7	11,8-18,1%
IgA	0.6	0.6	0.4	n.a.	0.4	0.4	0,7-4 g/l
IgM	n.a.	0.3	0.1	n.a.	0.1	0.1	0,4-2,3 g/l
IgG	n.a.	5.3	4.1	n.a.	3.9	3.3	7-16 g/l

Abbreviations: GGT: Gamma-Glutamyl-Transferase; GOT: Glutamate-Oxalacetate-Transaminase; GPT: Glutamate-Pyruvate-Transaminase; Ig: Immunoglobulin; n.a.: Not Available. Parameters that do not match the standard range are indicated in bold numbers. Oct 05 first diagnosis of CLL, Jan 08 begin of Amanita therapy, Sep12-Jun15 additional Chelidonium treatments

3. RESULTS

With variable doses of Amanita the patient now is stabilized for nearly eight years until today. Higher doses lead to cell digestion, leukocyte level decreases and LDH increases. During the therapy a side effect appeared: The effect of the drug – digestion of tumor cells - correlate with energy consumption and the patient frequently was tired. No other repetitive side effect

occurred. Due to his vegetarian diet, he in addition suffered from low iron levels.

The patient often suffered from swollen fingers in phases where cells are digested. This could show an involvement of the kidney in that process: Larger cell debris could plug it. In March 2010, the serum showed once haemolytic effects. This was due to a high LDH level of 376 U/l in a phase where leukocyte levels decreased.

In November 2011 lymph node swelling occurred together with an enlarged spleen. These symptoms vanished after three months.

In April 2012 leukocyte levels decreased from 169 LEU to 139 LEU without elevation of the Amanita dosage. The patient was riding daily 30 minutes on his racing bicycle during this time. During other periods with intensive exercises, positive effects could be repeated in September and December 2014. With sport activities, tumor growth can be diminished, and lower doses of Amanita can be applied for stabilization.

High levels of creatinine showed an involvement of the kidney beginning of 2013. The patient got infusions with a mixture of homoeopathic drugs. These infusions were stopped and creatinine levels normalized again until March 2013. In April 2013 a basaliome on the head was diagnosed. Excision of the 2 x 1 cm large tissue and pathologic inspection revealed a cutaneous marginal cell lymphoma (ICD-0, ICD-10, C44.9, pT1G1; 90% of the cells showed CD20 and CD79a expression, no CD3 or CD5 expression; with bcl2 positive and bcl6 negative genotype. Proliferation is mediate according to parameter Ki67).

During the tumor therapy with Amanita, continuously higher doses of the drug were necessary for stabilization. In addition, thrombocyte levels decreased continuously. Therefore a combination therapy was applied. Therapy with *Amanita phalloides* (zertifiziert nach Riede) D2 (4 x 10 drops per day) plus *Chelidonium majus* D1 (2 x 10 drops per day) started in August 2013 (Fig. 2). After a month the thrombocyte level remained constant, leukocyte level and LDH increased. After the second month, thrombocyte levels decreased, with still increasing LDH and leukocyte levels. This first Chelidonium pulse was completed, and Amanita was reduced to 3 x 10 drops per day. The thrombocyte level increased, and leukocyte levels further decreased.

In November 2013 the patient suffered a cystitis followed by antibiotic treatment. In October and November 2014 an antibiotic treatment occurred due to a common cold. In February 2015 he suffered from inflammations of the oral mucosa. He was stressed from his work.

A second therapy pulse with additional Chelidonium started in April 2015 (Fig. 3). The leukocyte level first increased then decreased again. LDH levels first dropped and then

increased again. These reactions are different than during the first pulse. Only the thrombocyte level showed a similar profile after both Chelidonium pulses. In both cases the level regenerated significantly.

Regular monitoring of laboratory parameters revealed, that none of the therapies induced liver damage (Table 1). All liver parameters (GGT, GPT, GOT, Cholinesterase and Glutamatdehydrogenase) remained constant within the normal range. Within the red blood system basically no aberration occurs. Within the white system, an initial deprivation of protein in serum, combined with immunoglobulin deprivation and albumin overexpression occurs. These irregularities were not influenced by the therapies. This indicates that the effect of Amanita and Chelidonium interferes only with the regulation of cell growth but not with other biochemical irregularities.

Regular oncologic monitoring including ultrasonic examinations occurred. So far, a spleen enlargement to 154 mm length (June 2015) was diagnosed. No lymph node involvement, heart or lung dysfunction, or other irregularities could be detected.

Amanita and Chelidonium Pulse 1

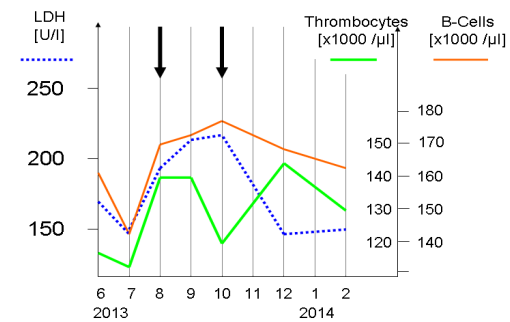


Fig. 2. Amanita plus Chelidonium

Shown is the first interval of Chelidonium uptake (between arrows) in 2013. The red line indicates leukocyte levels, the blue dotted line LDH levels, and the green line thrombocyte levels

4. DISCUSSION

The goal of a good tumor therapy is to keep the patient in life at life. Here a patient with a diagnosed CLL could be kept stable for nearly eight years until today, basically with one major anti tumor drug: *Amanita phalloides* in the appropriate dilution. To avoid complications, like the upcoming thrombocyte deprivation, additional *Chelidonium majus* was applied. Whereas no

reproducible effect on tumor cell growth or cell destruction could be observed, reproducibly a positive effect on thrombocyte levels was observed. This can lead to the conclusion, that a Chelidonium pulse can be applied whenever neoplastic cells suppress growth of other blood cells.

Amanita and Chelidonium Pulse 2

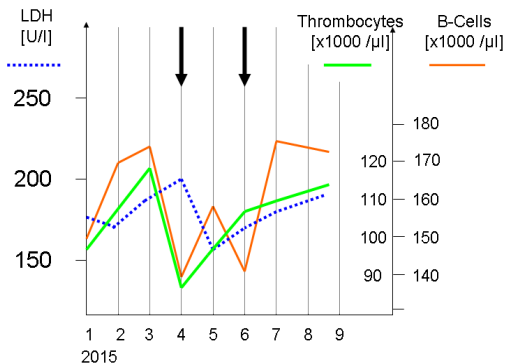


Fig. 3. Amanita plus Chelidonium

Shown is the second interval of Chelidonium uptake (between arrows) in 2015. The red line indicates leukocyte levels, the blue dotted line LDH levels, and the green line thrombocyte levels

Why is Chelidonium not applied continuously? Chelidonium is a strong therapeutic impulse for the cells. It is as well able to induce hepatitis, possibly due to activation of silent viruses. As well it could be observed, that local application can activate a silent varicella zoster virus infection (own observations). Due to these possible complications, this drug is applied in only small doses for only a short pulse to avoid secondary effects as far as possible. In addition no selective pressure should be induced, any rescue drug is invaluable during a tumor therapy over years.

Any drug can lead to resistance mutations in the cells. With a standard mutation rate of $1:10^6$, drug resistance is expected to occur within weeks. But after years of therapy with *Amanita phalloides* the drug still is able to diminish growth of tumor cells in this patient. This might be due to the low concentration of the drug: It is applied not to poison the tumor cell, but to reprogram it at the molecular switch to tumor formation. Therefore no selective pressure is induced here.

5. CONCLUSION

The results presented here suggest following tumor therapy:

Amanita as a permanent drug reprograms the tumor cell and reduces tumor cell activity. A pulse of additional Chelidonium can diminish secondary effects of tumor growth. Intensive exercises lead repeatedly to lower leukocyte levels, or to lower Amanita dosage. This indicates that all therapy management should - in addition to dietary recommendations - include a sport program for the patient. With this therapy no hospitalization of the patient is needed, he stays in life at life.

CONSENT

Author declares that written informed consent was obtained from the patient for publication of this case report.

ETHICAL PERMISSION

Only existing drugs in usual doses are used during this study. No new drug was applied. Therefore no ethical permission is necessary in this case.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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