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A Specific Mistletoe Preparation (Iscador-Qu®) in Colorectal Cancer (CRC) Patients: More than Just Supportive Care?

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Abstract

Rationale: In 2009 we reported the results of a pharmaco-epidemiological, retrospective observational cohort study in colorectal carcinoma (CRC) patients UICC stage I-III, receiving chemo- and/or radiotherapy together with European Viscum album L. ("Viscum") extract (Iscador®) as supportive care (n = 429) versus the conventional treatment (n = 375) after R0 resection (J. Soc. Int. Oncol. 7: 173-145). The endpoints have been therapy induced adverse effects, disease symptoms and disease-free survival (DSF).

Objective: Here, we present the secondary and confirmatory analysis of this original data set with respect to the host tree specificity of Viscum.

Results: Patients receiving the extract from Viscum harvested from oak (Quercus) trees, Iscador® Qu (Isc-Qu), in a supportive care mode simultaneously with chemo- and/or radiotherapy (n = 106) showed a significant improvement in therapy induced adverse effects, and, most remarkable, a significant delay of metastasis formation and longer DFS compared to conventionally treated patients (n = 212) (control). To make the analysis more robust, patients treated by the chemo- and/or radiotherapy protocols were also analyzed and stratified for the UICC I-III stages. Accordingly to the overall Kaplan-Meier analysis result, patients receiving Isc-Qu as supportive care presented significantly longer median time to distant metastases formation (metastasis-free survival, MFS) within the course of the observational cohort study (133+ months (Isc-Qu) versus 94 months (control), p (Log Rank) = 0.002. In the Cox regression analysis, the confounder-adjusted hazard ratio, HR, (95% confidence interval) came up to HR (metastasis) = 0.31 (0.13-0.711), p = 0.006. This result indicates an estimated 69% metastasis-hazard-reduction in the Isc-Qu group relative to the controls. In summary, patients concomitantly treated by Iscador® showed fewer persisting disease- and therapy-induced symptoms and the DSF hazard ratio suggested a survival benefit.

Clinical implication: This secondary and confirmatory analysis of the original data set suggests that a mistletoe (Viscum) preparation, harvested from oak (Quercus) trees (Isc-Qu), appears to be a naturally tailored molecular composition to target CRC patients by reducing therapy-related adverse effects, improving the cancer-related symptoms and showing a potential to increasing the metastases-free survival.

Limitations: The effect on prolonged survival should be interpreted with some caution because the applied study design shares some potential risk for bias common to all non-randomized observational studies. Also, potential biases were tried to minimize by systematic multivariable adjusting of end point criteria for baseline imbalance, treatment regimen, and other potential confounders.

Keywords: CRC patients; Therapy-induced adverse effects; Metastasis-free interval; Iscador®-Qu; Viscum; Chemo-/Radiotherapy; Supportive care

Introduction

Supportive care is not a new discipline in modern medicine. The concept of continuous best supportive care (BSC) for diseased people is an ethical must and cannot be neglected within integrative, multidisciplinary and personalized treatment regimens. Supportive care is a complex network of all care giving and supports necessary for ill people, at the same time as specific treatment occurs, along all severe illnesses [1]. The concept of BSC is of special interest in oncology because it is focused on prevention of the most burdensome symptoms like nausea, vomiting, fatigue, pain, neurotoxicity, anemia and neutropenia in patients receiving chemotherapy, radiation treatment and also targeted immunotherapy. BSC also includes psycho-oncology treatment, nutritional and social care. As cancer is predominantly an illness of elderly people, the topic of BSC is very timely, because many elderly people are co-morbid. As the size of the older population is increasing throughout the world, cancer incidence is also steadily increasing and the treatment of older patients, concomitantly suffering from co-morbidity, should be as effective as it is in younger ones. Age must not be a contraindication of the state-of-the-art of primary anti-tumor therapy as long as it is based on physiologic age and appropriate BSC is provided [2].

Till death do us part: best supportive and palliative care

Complementary and alternative medicine (CAM) is a big issue

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for cancer patients. In particular, "alternative cancer cures" are being promoted to vulnerable patients. However, none of these "cures" have been shown to do what they promise. Yet CAM can play an important role in oncology, and that is in supportive and palliative care [3]. Standardized integration of supportive and palliative care into comprehensive cancer therapy needs an early common sense of the patient with the physician and any other care givers to identify disease-specific physical, mental and social restrictions in order to cope with the needs of daily life [4]. There is an interface between medical oncology and supportive and palliative care, which has to be explored early in each cancer disease trajectory for the benefit of the patient [5]. Evidence-based guidelines in clinical oncology practice are now prominent; given the complexity of cancer management, a multidisciplinary approach is essential in order to address the production of guidelines for supportive care by interdisciplinary teamwork [6].

In Switzerland, the Society for Cancer Research (Verein für Krebsforschung) has a long tradition on CAM and promotes basic and clinical mistletoe research in the Institute HISCIA (Arlesheim). The generated research data are integrated into clinical settings by the associated Lukas Clinic located in Arlesheim (Basel). The Clinic also adapts the vision of the American Society of Clinical Oncology (ASCO) for improved communication with and decision making for cancer patients [7]. It advocates an individualized approach to discussing and providing disease-directed BSC options for cancer patients. It is important to possess a solid understanding of how to prevent and treat adverse effects of an anti-tumor therapy, because proper BSC helps patients with cancer to live longer, happier and healthier lives [8].

Toxicities and morbidities are among the biggest hurdles for a cancer patient to face chemo- and radiotherapy, as well as targeted cancer-immunotherapy. Advances have been made in delivering BSC to address cancer treatment toxicities and complications [9].

Learning from the past will go into the future

We have recently shown in CRC patients undergoing chemo-/radiation therapy, that mistletoe (Viscum) preparation Iscador® is an essential BSC drug when included into conventional therapy regimens or administered as aftercare treatment, because adverse effects of the primary therapy were substantially reduced and disease-free-survival (DFS) statistically significantly extended [10].

According to Good Epidemiological Practice rules (GEP), here, we report a secondary confirmative analysis using the original data set of this afore mentioned cohort [10], in order to figure out what host-specific tree of mistletoe preparation should be recommended best for supporting simultaneously chemo- and/or radiotherapy protocols in non-metastatic CRC patients to cope with toxicities and complications, to increase quality of life and metastases-free survival.

Study Desing, Methods, Patients and Material

Study design

The study design and methods have been described in detail recently [10]. In short, a multicenter, retrospective, comparative, observational cohort study was carried according to GEP and obeying the European directives 2001/83/EC and 2001/20/EC including all amendments. The cohort study was a non-interventional study and original medical records of eligible patients were used to collect anonymous data on the supportive care treatment with Isc-Qu versus no mistletoe application during the primary and/or the aftercare period.

Isc-Qu was administered by 2-3 weekly subcutaneous injection, and the therapy regimen was left at the discretion of the treating physician. The treatment was finalized before study commencement.

The patients' data collections started in the past, at the time of diagnosis and/or surgery of the primary tumor and continued forward in time, meeting pre-specified clinical targets – namely therapy induced adverse effects, symptoms and metastases-free survival.

Methods

For statistical analysis the data subsets of chemo- and/or radiotherapy-treated patients who received in a supportive care intention simultaneously Isc-Qu were used and compared to patients´ data obtained from the original control cohort patients, who did not receive any mistletoe treatment. A confounder-adjusted odds ratio (OR) calculated by the logistic regression was used to measure the effects on therapy-induced adverse reactions and on symptoms, while a confounder-adjusted hazard ratio (HR) was calculated for metastases-free survival by the Cox proportional hazard regression method (Cox regression).

Bias management

Non-randomized studies carry the risk of confounding biases, e.g. due to baseline data imbalances or different therapy regimens. Therefore, all end-point results were adjusted for pre-defined confounder effects: age, sex, study centers, co-morbidity, tumor localization, UICC/AJCC tumor stage, histo-pathological tumor grading, postsurgical staging, chemotherapy, duration and dosages of chemotherapy applied and concurrent radiotherapy. The results were re-confirmed by sensitivity analyses using pre-defined multivariable models and adjusting procedures [11-13].

Patients

The data from three hundred and eighteen (318) consecutive CRC patients of UICC stage I-III, who underwent a radical resection (R0) were eligible from the original data set to perform the secondary, confirmative analysis. One hundred and six (106) non-metastatic CRC patients received Isc-Qu in addition to the conventional, adjuvant chemo- and/or radiotherapy protocol; two hundred and twelve patients (212) from the same patients' cohort served as a control group.

Material

The supportive care treatment was carried out with commercially available batches of Isc-Qu dosages that were given simultaneously to standard chemo- and/or radiotherapy protocols. Isc-Qu preparations are aqueous extracts from the mistletoe plant (*Viscum album L., ssp Album*) originated from different host trees manufactured according to specific guidelines The Isc-Qu used in this study is extracted from the mistletoe of the oak tree (Qu = Quercus). Therefore, one and two years old mistletoe leaves, stems and berries are harvested in summer and in winter. The fresh plant is fermented with special starter cultures (*lactobacilli*) and the aqueous extracts are then blended on a complex machine, resulting in the preparation of Isc-Qu (DEV = 1:5). Through this special blending method, the typical composition and quality of Isc-Qu is formed. The drug substance Isc-Qu is diluted with isotonic saline solution, sterile filtered and subsequently filled into ampoules as an aseptic injection preparation. In order to ensure consistent quantity of ingredients and quality, the typical proteins (mistletoe lectins and viscotoxins) are determined.

Working hypothesis

The aim of this secondary and confirmatory analysis was to examine the hypothesis whether Isc-Qu can be integrated as BSC and concomitantly administered during chemo- and/or radiotherapy regimens for R0-resected CRC patients. The analysis should clarify whether chemo- and/or radiotherapy plus Isc-Qu is superior to chemo- and/or radiotherapy alone in respect to oncologic therapy-induced adverse effects, disease-related symptoms and to prolongation of metastases-free survival due to this particular host tree-specific mistletoe preparation.

Results

The baseline demography and diagnostic criteria of the subgroups are summarized in Table 1 and the treatment regimens are documented in Table 2.

The median follow-up for the Isc-Qu group was 59 months versus 43 months in the control group. Within the Isc-Qu group there were more males and at a younger mean age than in the control group. Tumor staging and grading revealed more patients with advanced disease in the Isc-Qu- than in the control group; more patients with additional diseases (multi-morbidity) were included in the control group. In both groups, all patients were mainly treated with a 5-FU-based therapy, which was in rare cases given in combination with cis-platin drugs (2.8% versus 5.2%). In addition to a chemotherapy protocol, radiotherapy was frequently applied in rectal cancer patients

Baseline demographic and prognostic criteria (subgroup analysis with simultaneous ISC-Qu) initial sample size 318 (106 vs. 212)	Value (test) ISC-Qu group % or mean (± SD)	Value control group % or mean (± SD)	Valid N test / control group	p-values (Chi-Square, exact Fisher's, or Mann-Whitney-test)
Age at onset of aftercare; mean,(SD) years:	53.7 (10.9)	58.3 (9.5)	106 / 212	0.001
Body weight; mean, (SD) kg:	73.9 (9.9)	76.8 (13.7)	101 / 206	0.147
Body height; mean, (SD) cm:	177.4 (7.3)	171.5 (8.6)	105 / 208	<0.001
Gender males / females %	76.4 / 23.6	56.6 / 43.4	106 / 212	0.001
Tumor stage "high-risk" (T3 / T4) %	67.0	72.0	106 / 211	0.364
Tumor stage node positive (N1/2) %	78.3	41.7	106 / 211	<0.001
Tumor stage grading (G3/G4) (highly malignant) %	42.9	15.2	105 / 211	<0.001
Tumor stage UICC III (advanced) %	78.3	41.7	106 / 211	<0.001
Tumor localization colon or rectal, %	55.7 / 44.3	60.7 / 39.3	106 / 211	0.400
Tumor postsurgical completely removed (CR, NED) %	96.2	94.0	106 / 200	0.591
Symptoms present at baseline %	94.3	74.5	106 / 212	<0.001
Other concurrent diseases (multi-morbidity) present %:	43.8	64.1	105 / 206	0.001
1st surgery to ONC therapy begin time; mean, (SD), months	1.0 (6.8)	3.4 (7.8)	106 / 211	<0.001
Aftercare / follow-up duration up to the last information; mean (SD), and median (range), months	59.1 (25.6) 59 (11-155)	49.9 (25.1) 43 (2-144)	106 / 210	<0.001

SD (standard deviation)

Table 1: Demographic data, tumor staging and co-morbidity.

Treatment regimen (subgroup analysis with simultaneous ISC-Qu) (initial sample size 318 (106 vs. 212))	Value (test) ISC-Qu group % or mean (± SD)	Value control group % or mean (± SD)	Valid N test / control group	p-value (Chi-Square, Fisher's or Mann-Whitney-exact test)
Radiation therapy received % (including any combination)	40.0	29.2	105 / 212	0.058
Chemotherapy received % (including any combination)	98.1	94.8	106 / 212	0.232
Chemotherapy: 5-FU / pyrimidines %	97.2	93.4	106 / 212	0.194
Chemotherapy: platin-based drugs %	2.8	5.2	106 / 212	0.400
Chemo- / radiotherapy (ONC) % Only radiotherapy % Only chemotherapy % Chemo- and radiotherapy combined %	100.0 1.9 60.0 38.1	100.0 5.2 70.8 24.1	105 / 212 2 / 11 63 / 150 40 / 51	0.023
Chemotherapy: 1st course duration: mean (SD), (months)	5.2 (3.3)	5.8 (3.1)	104 / 198	0.006
Chemo-/radiotherapy (ONC) total duration: mean, (SD), (months),	8.5 (11.5)	8.7 (12.4)	106 / 204	0.059
ISC-Qu: overall therapy duration: median, (range), (months)	54 (11-141)	n/a	106	n/a
Cumulative ISC-Qu dose (mg): mean (SD), [median (range)]	4299 (2349) [4221 (696-10523)]	n/a	106	n/a
Estimated mean weekly ISC-Qu dose (mg), mean (SD), [median (range)]	16.2 (6.4) [17 (2-37.7)]	n/a	106	n/a

Table 2: Conventional Treatment regimens and Iscador®-Qu dosing.

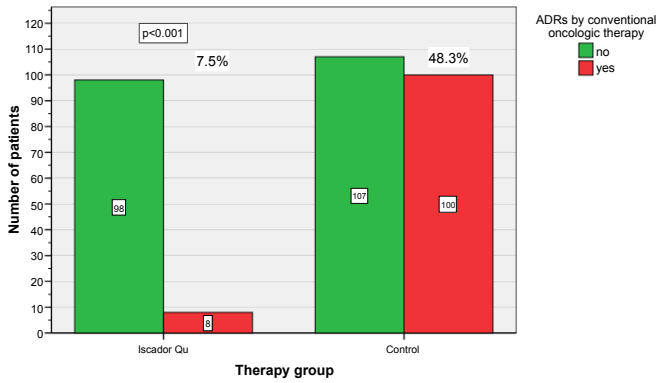

Figure 1: Comparison of the conventional treatment group obtaining supportive Iscador®-Qu care (left) with the conventional therapy only (right) in respect to the number of patients with therapy-induced adverse reactions (ADR) (green, no; red, yes).

according to standard procedures. More rectal cancer patients received radiotherapy in the Isc-Qu than in the control group (40% versus 29.2%).

The intervention treatment and follow up period amounted to 11-141 months (median 54 months) and the total cumulative dosage of Isc-Qu in an intended supportive care mode given subcutaneously 2-3x times weekly added up to median 4,221 mg, (range 696-10,523 mg). The estimated mean weekly Isc-Qu dose resulted in 16.2 mg.

The median duration of the 1st course of chemo-, and/or radiotherapy was approximately 5 months in both therapy groups.

Cancer therapy induced adverse effects (ADR)

Significantly fewer patients in the Isc-Qu- than in the control group showed cancer therapy induced ADR. Ninety-eight pts. did not show therapy-related side effects, while 8 pts. (7.5%) showed undesirable side effects (Figure 1). In the control group, treated only with conventional protocols, 112 pts. (48.3%) experienced treatment-related side effects, while 100 pts. did not report therapy-related side effects (p<0.001).

The confounder-adjusted odds ratio for the ADR-chance after the end of the 1st therapy course at median 5 months in both groups (i.e. the estimated chance to encounter at least one ADR in the Iscador-Qu- relative to the control group during this time interval) revealed an OR = 0.10 (0.04-0.26), p<0.001. This means an estimated ADR-chance-reduction by 90% in the Isc-Qu- relative to the control group.

In particular, during the course of the therapy regimen with chemo- and/or radiotherapy, pts. receiving Isc-Qu as supportive care have long-lasting significant benefits in respect to clinical symptoms, like nausea and vomiting, loss of appetite, fatigue, depression, sleep disturbances and mucositis.

The overall symptom score, i.e. the number of patients with at least one disease- or treatment-induced symptom at the end of the 1st therapy course, showed 43.4% in the Isc-Qu group compared with 85.1% in the controls, p<0.001. This effect persists even after the adjusting for confounders, revealing the adjusted odds ratio of OR = 0.10 (0.03-0.33), p<0.001 (Figure 2).

Delay of metastasis formation (Metastasis-free survival Mfs)

Metastasis formation is the main cause of mortality in CRC.

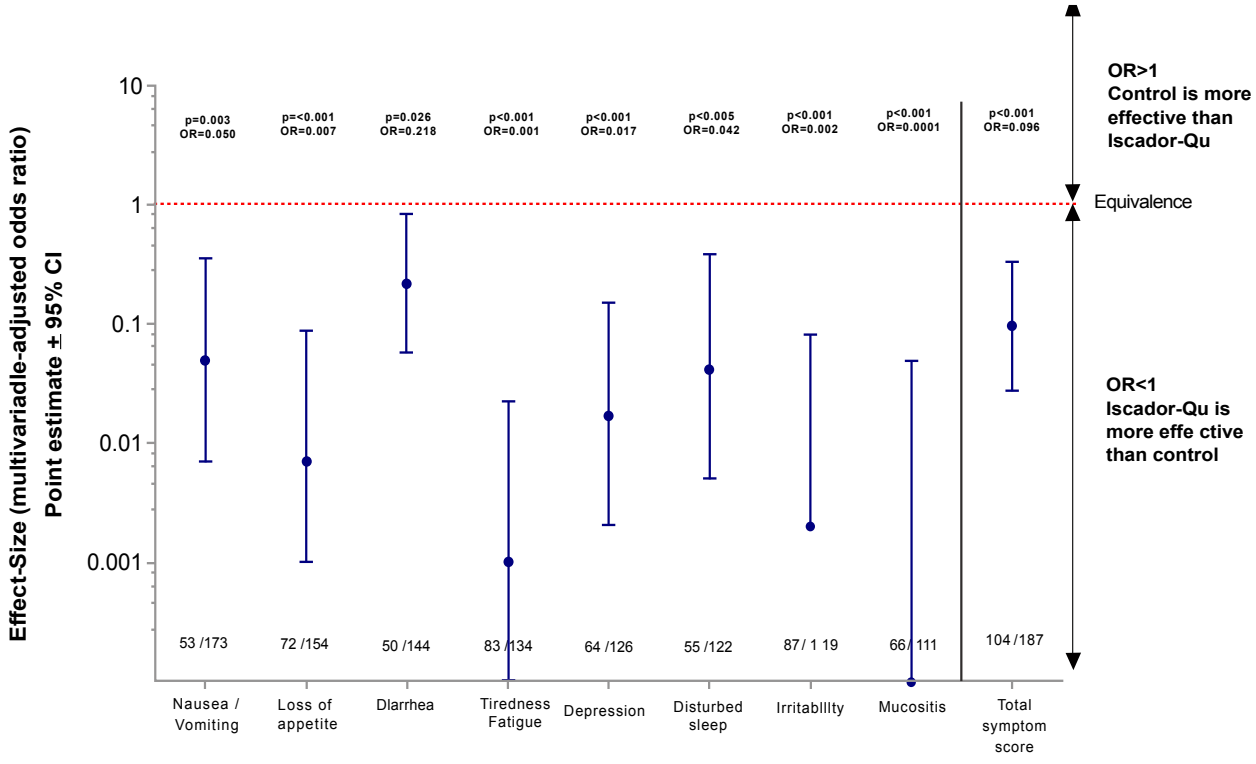

Figure 2: Detailed symptom persistence analysis after a median 5 months therapy course. The x-axis nominates the single symptoms and the total number of patients evaluated with the different symptoms. The logarithmic y-axis nominates the multivariable-adjusted odds ratios (OR). The dots show the OR point estimates and the bars the 95% confidence intervals of OR.

Therefore, there are worldwide ongoing efforts to find drug-based strategies, to inhibit or at least to delay the onset of metastasis formation. Figure 3 shows a Kaplan-Meier analysis and Figure 4 shows the confounder-adjusted Cox proportional hazard regression analysis of all evaluated pts. (n = 318) for the outcome endpoint "metastasis-free survival" (MFS). The supportive care application of Isc-Qu surpasses the treatment results of the control group, which did not receive Isc-Qu. The clinical result showed a significantly prolonged delay of metastases formation, when chemo- and/or radiotherapy and Isc-Qu are administered together within one treatment schedule. In the Kaplan-Meier-analysis, the median MFS was 133+ (Isc-Qu) vs. 94 (control) months (p-Log Rank = 0.002). In the Cox regression, the confounder-adjusted hazard ratio HR (i.e. the estimated relative hazard with 95% confidence intervals) to encounter a distant metastasis in the Isc-Qu group in the course of the study as compared to the controls amounted to HR = 0.31 (0.13-0.71), p = 0.006. This result indicates an estimated MFS-hazard reduction of 69% in the Isc-Qu- relative to the control group.

The MFS was evaluated in more detail by stratification analysis according the UICC tumor stage I-III. Particularly striking were the results in advanced CRC (UICC stage III), where those pts. supported by Isc-Qu (n = 83) and pts. only receiving chemo-and/or radiotherapy (n = 88) were almost equally distributed between chemo-and/or radiotherapy treatment. In this advanced UICC stage subgroup, 13 (15.7%) pts. in the Isc-Qu group and 43 (48.9%) pts. in the control group were diagnosed with distant metastases in the course of the study (p<0.001) (Table 3a). The statistical analysis exhibited for all evaluated UICC-stages differences towards a benefit in respect to delay of metastasis formation, when Isc-Qu was included simultaneously as supportive care in standardized chemo-/radiotherapy protocols for CRC pts (Table 3b).

Considerably, however, in the advanced UICC stage III, a statistically significant and clinically relevant lower incidence and longer delay of the distant metastases formation were found in the ISC-Qu group, when compared with the controls (p<0.001).

Discussion

An optimal supportive care is accepted as a fundamental objective

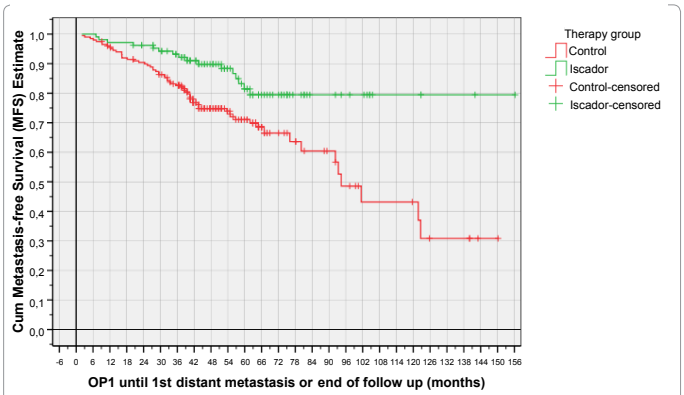

Figure 3: Kaplan-Meier analysis of metastases free survival of all patients (n = 318, UICC stage I-III). The green line denominates the patients receiving simultaneously to the conventional chemo- and/or radiotherapy a supportive Isc-Qu care. The red line denominates the control patients being only treated by conventional chemo- and/or radiotherapy. The median time to the first distant metastasis (i.e. the metastasis-free survival, MFS) was 133+ months in the Isc-Qu group, versus 94 months in the control group (p-Log Rank = 0.002).

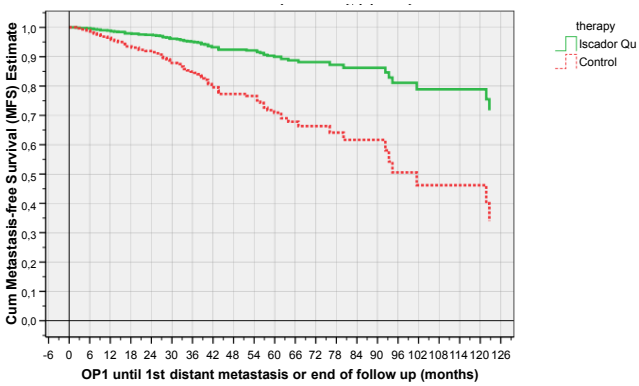

Figure 4: Confounder-adjusted Cox proportional hazard regression analysis of metastases free survival in all patients (n = 318, UICC stage I-III). The green line denominates the patients receiving simultaneously to the conventional chemo- and/or radiotherapy a supportive Isc-Qu care. The red line denominates patients being only treated by conventional chemo- and/or radiotherapy. The hazard ratio (95% confidence intervals) was: HR = 0.31 (0.13-0.71), p = 0.006. HR indicates the confounder-adjusted hazard ratio (i.e. the estimated adjusted relative hazard to develop a distant metastasis in course of the study in the Isc-Qu group compared with the control group).

UICC-tumor stage	Therapy group	Total N	N of Events	Censored	
				N	Percent
0-I	Iscador Qu	13	0	13	100.0%
	Control	42	8	34	81.0%
	Overall	55	8	47	85.5%
II	Iscador Qu	10	3	7	70.0%
	Control	70	11	59	84.3%
	Overall	80	14	66	82.5%
III	Iscador Qu	83	13 (15.7%)	70	84.3%
	Control	88	43 (48.9%)	45	51.1%
	Overall	171	56	115	67.3%

Table 3a: UICC tumor staging and metastases formation (number of events).

UICC-tumor stage		Chi-Square	df	Sig.
0-I	Log Rank (Mantel-Cox)	2,756	1	.097
	Breslow (Generalized Wilcoxon)	2,041	1	.153
	Tarone-Ware	2,408	1	.121
II	Log Rank (Mantel-Cox)	,598	1	.440
	Breslow (Generalized Wilcoxon)	,881	1	.348
	Tarone-Ware	1,063	1	.303
III	Log Rank (Mantel-Cox)	21,162	1	**.000**
	Breslow (Generalized Wilcoxon)	19,625	1	**.000**
	Tarone-Ware	20,545	1	**.000**

Table 3b: Statistical analysis of the events (metastases formation) stratified by the UICC tumor staging Case Processing Summary.

in clinical oncology and it is an ethical need for cancer patients. Very recently the therapeutic potential of anamorelin in patients with cancer-related cachexia was shown [14]. There is also a need of newly diagnosed cancer patients attending a regional cancer center to determine and plan supportive care strategies [15]. Therefore, we already published the clinical effects of supportive mistletoe treatment in colorectal patient [10]. In general, mistletoe preparations (Viscum album L.) are highly debated in clinical oncology. However, if clinical trials are bringing substantial supportive benefit, as already shown for Iscador (Viscum album) in colorectal [10] and pancreatic tumor

patients [16], this supportive drug (Viscum album) presents an entirely new indication of significant therapeutic interest.

Here, we report in more detail and, according to good clinical practice, a second, supportive and confirmatory analysis about the clinical and pharmaco-epidemiological specificity of a mistletoe preparation derived from the host tree oak/*quercus* (Qu). Previous data have been shown that Viscum album preparations were able to inhibit the *in vitro* growth of carcinoma cells and the extent of this inhibitory effect varied with the mistletoe host tree [17]. There are different Viscum album preparations from different host trees with biomodulating effects available, obtained from mistletoe growing on apple tree, *malus*, (M) on pine, *pinus*. (P) or white fir, *abies*, (A). One of the working hypotheses is that the mistletoe lectin content determines the magnitude of the biological response. It has been demonstrated *in vitro* that mistletoe lectin ML-I and ML-II enhance the cytotoxic effect of chemotherapeutic drugs and activate caspase-8/FLICE [18], inhibit tumor angiogenesis [19] and exerts anti-inflammatory effects by selectively inhibiting cytokine-induced expression of cyclooxygenase-2 [20]. Data on the gene expression profile in breast cancer cells indicate that mistletoe from the host tree *abies* affects the cell-cell adhesion and genes involved in pathways of the cytoskeleton signaling [21], which might result in reduced cellular locomotion [22], one prerequisite of diminished metastases formation. Isc-Qu and Isc-M mainly modulate gene responses attributable to immune defense and stress response genes [21].

It is too preliminary in pharmacological *European Viscum album L.* research to state that the mode of action is due to the lectins and their concentrations, because other compounds, like viscotoxins, are also pharmacologically active ingredients. Therefore, it is important to investigate the pharmaceutical mistletoe preparation frequently for these active compounds, which show seasonal fluctuations and which demands therefore for fixed harvesting seasons [23].

It is very plausible to explain in an associative mode the observed clinical results when Isc-Qu is added simultaneously to conventional chemo- and/or radiotherapy protocols. The clinical results have enabled us to create a model for its mode of action as a robust working hypothesis. According to this model, the multidrug components of this specific Viscum album preparation i) are likely to increase the cytotoxic potential of chemotherapeutic drugs, ii) increase the apoptotic activity within the tumor parenchyma, iii) decrease the angiogenic potential of tumor-associated endothelial cells and upregulate an anti-tumor gene profiling. Moreover, a genetically induced profile, which counteracts tumor cell singularization or small tumor cell cluster formation together with cell motility inhibition are mandatory for the inhibition of metastasis formation. The observed diminished adverse therapy induced effects might be due to the selective inhibition of Cox-2, but the selective inhibitory activity of ISCADOR-Qu® is also likely to contribute to an anti-tumor effect, because it is well documented that a higher expression of COX-2 can be found in invasive squamous carcinomas *in vivo* [24,25].

The most intriguing outcome is demonstrated by the Kaplan-Meier analysis concerning the metastasis-free survival (Figure 3). The result is further substantiated, if the patients are stratified according to the UICC staging I to III (Table 3). At the time of diagnosis stage I to III patients do not show up clinically with distant metastases, although lymph node metastases are present (IIIa/N1; IIIb/N1; IIIc/N2).

Tumor metastases are responsible for approximately 90% of all solid cancer-related deaths. A functional molecular network contributes to the development of a selective environment that promotes the seeding and malignant progression of metastatogenic cells in distant organ. There are gene candidates and proteins and signaling pathways that are under clinical investigation. Target therapies for the treatment of cancer and inhibition of metastases formation are going to revolutionize concepts in oncology. However, a single-target therapy is fading out in favor of a multi-target approach. The prevailing idea is to have a selective cocktail of the next generation drugs or reminiscent of conventional agents which are known to have several targets, or, as shown here, a composition of well-defined nature tailored plant derived molecules as present in Viscum album (Isc-Qu).

In this view, there is now a general agreement that molecules interfering simultaneously with multiple pathways might be more effective than single target agents. Such a scenario is emerging by Viscum album; because the ingredients are able to inhibit more than one pathway and the clinical results are the potentials to cope with therapy induced adverse effects and they are able to delay metastases formation. The research protocols to evaluate the different host tree specific Viscum album (Isc-Qu) preparations in respect to personalized medicine [26] and tumor specific activities are just opened.

Here, we report for the first time in a well-defined and confirmatory subgroup analysis of CRC patients that a specific Viscum album preparation (Isc-Qu), when simultaneously administered in a supportive setting with conventional chemo- and/or radiation treatment, decreases therapy induced adverse effects, and, most impressive, induces a delay in metastases formation.

Isc-Qu is a first supportive care candidate to be included into conventional chemo- /radiation therapy protocols for colorectal patients to decrease the rate of treatment deviations due to therapy induced adverse effects, above all in elderly and often comorbid patients [27] and likely getting a concomitant benefit from the metastases prevention potential of this specific Viscum album preparation.

Disclosure of Interest

BPR and HJ received a research grant from HISCIA, Switzerland (Society for Cancer Research).

MH and ZKS declare that they have no competing interests.

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