Targeting Inflammation in Cancer-Related-Fatigue: A Rationale for Mistletoe Therapy as Supportive Care in Colorectal Cancer Patients

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Abstract: *Background*: Cancer-related fatigue (CRF) affects a majority of patients (pts) with symptoms lasting up to several years after finishing therapy. These symptoms lead to decreased health related quality of life. Fatigue during treatment for colorectal cancer is common, but poorly understood and can affect compliance with post-surgical cancer therapy. We examined the fatigue levels during first-line chemo- or radio-chemotherapy protocols, which were supported by a pharmaceutical mistletoe preparation (Iscador®Qu) (181patients). We compared the outcome to a parallel control group (143 patients), which did not receive this supportive care treatment. *Methods*: The medical records of 324 patients with non-metastasized colorectal cancer (UICC stage I - III), which were obtained from hospitals and resident physicians, were assessed. The documented treatment decision by chemo- or radio-chemotherapy supported by mistletoe interventions was followed for a median treatment period of 8.6 months. During the post-surgical treatment period the patients were diagnosed twice for the presence of fatigue symptoms by structural interviews carried out by physicians. *Results*: At the end of the median treatment period, 16/181 patients (8.8%) were diagnosed with CRF in the supportive care group and 86/143 (60.1%) in the chemo – or radio-chemotherapy group without supportive mistletoe medication. Multivariable-adjusted ORs provided evidence for a chance to improve CRF by supportive mistletoe medication compared to chemo- or radio-chemotherapy alone over the time of treatment. The OR = 10.651 (95% CI 5.09-22.28; $p < 0.001$) declined from the first visit to OR = 0.054 (95 CI 0.02-0.13; $p < 0.001$) at the end of therapy. Furthermore, 14 confounding factors for risk assessment of CRF were compared by means of forest plots. It turned out that the hospital versus office-based treatment and the co-morbidity/inflammation represent independent but important determinants for fatigue levels. *Conclusion*: The clinically used mistletoe medication (Iscador®Qu) is the first candidate to be included in a supportive care modus into chemo- or chemo-radiotherapy protocols for colorectal patients to improve CRF without discernable toxicities.

Keywords: Cancer-related fatigue, colorectal cancer, chemo-radiotherapy, Iscador®Qu therapy, inflammation, supportive care, quality of life.

INTRODUCTION

Cancer-related fatigue (CRF) is a disabling and distressing symptom complex that is highly prevalent across the cancer continuum from a patient´s diagnosis and treatment through survivorship and end of life. It has a multi-faceted etiology and significant individual variability in its clinical expression, determinants, and sequelae. In short, CRF is defined as a subjective state of overwhelming sustained exhaustion and decreased capacity for physical and mental work, which is not relieved by rest [1, 2]. CRF differs substantially from the fatigue that accompanies everyday life, which is usually temporary and relieved by rest. The long-term sequelae can affect the patient´s health-related quality of life (HRQoL), and there is empirical evidence of an association between inflammation, HRQoL and survival [3, 4]. The assessment of personal perception and suffering related to CRF is an important component of the multidimensional assessment of CRF and will enable physicians and nurses to better understand and manage the patient´s suffering related to CRF. The purpose of this study was to assess in a cohort of colorectal cancer patients the prevalence and incidence of CRF and improvement/relief of CRF when undergoing chemo- or radio-chemotherapy supported by a pharmaceutical mistletoe preparation. The supportive care by mistletoe treatment started at the initial consult, when the diagnosis was made or surgery was carried out and continued until the end of the postoperative therapy regimens.

The results of this retrospective study might give a rationale to initiate a prospective study with established biomarkers for CRF and to integrate a phyto-pharmacologic remedy into postoperative chemo- or chemo-radiotherapy protocols and thereby improving individually [5] inflammatory activities and HRQoL resulting in decreasing CRF symptoms.

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STUDY DESIGN, PATIENTS, METHODS AND SUPPORTIVE THERAPY

Study Design

The design of the original study from which the patients´ data are extracted and analyzed for the course of CRF was described recently in detail [6, 7]. In short, a multicenter, retrospective, comparative and observational cohort study of non-metastatic colorectal cancer patients was carried out, obeying the European directives 2001/83/EC and 2001/20/EC including all amendments. Original medical records from eligible patients obtained from university and community hospitals, from tumor ambulatories and general practitioners were used and CRF relevant data sets were transcribed into clinical research files under the guideline of a clinical protocol. The patients´ data collection started in the past, at the time of diagnosis and/or surgery of the primary tumor (visit1) and continued forward within the postoperative 5-FU-based chemo- or chemo-radiotherapy period (visit2) until to the end of the postoperative 5-FU-based chemo- or chemo-radiation therapy (visit3). The timely interview data for visit2 were judged as valid and were transcribed into clinical research files when half of the planned chemo- (median 2.8 months) or chemo-radiotherapy (median 4.3 months) were administered. Visit3 was commenced at the end of the first-line postoperative chemo- (median 5.2 months) or chemo-radiotherapy (median 8.6 months) therapy. The data were strictly anonymously collected. After surgery of the primary, supportive care treatment started with the mistletoe preparation Iscador®Qu and continued during administration of the adjuvant first-line therapy period. The control group received only adjuvant chemo- or chemo-radiotherapy without any supportive care modalities; one pre-specified clinical protocol item was the follow-up of CRF until the end of the adjuvant chemo- or chemo-radiotherapy treatment.

Structured Interviews

At least a 25-minute diligent anamnesis interview, structured by a symptom checklist, was completed with the eligible patient at visit1, 2 & 3. The patient´s complaints related to CRF and clinical symptoms of inflammation were noted and it was to the discretion of the interviewing physician whether he diagnosed that the patient experienced CRF and/or signs of clinical symptoms of inflammatory processes that prevented her/him from daily routine and "normal" life. Patients reporting symptoms of fatigue or showing signs of inflammation at the time of the interviews were asked a series of individualized, biography-based questions to better describe their individual fatigue experience and its impact on HRQoL. The presence or the absence of CRF, diagnosed by the consulting physician was literally documented in the patient´s clinical record. The consulting physician was blinded, because the diagnosis with respect to CRF was made independently from the supportive treatment allocation (Iscador®Qu *vs* no Iscador®Qu (ISC®Qu)). These documented data were analyzed for the course of CRF from visit1 to visit3 and correlated to gender, age, comorbidity, chemo- or radiotherapy, tumor localization (colon *vs* rectal), tumor stage (UICC I – III) and histological tumor grading.

Patients (pts)

A total of 601 pts, diagnosed for non-metastasized colorectal cancer, were recruited from 22 medical centers [6, 7]. A number of 324 pts from this original data set [6] were retrospectively evaluated for the presence of CRF. Beginning at the initial consult (v1), 181 pts were treated by adjuvant chemo- or radio-chemotherapy protocols, supplemented in a supportive mode by ISC®Qu (supportive care group); 143 pts served as controls having received only adjuvant chemo- or chemo-radiotherapy (control group).

All patients (n = 324) were treated by surgery and mostly R0-resected. Ninety-seven percent of these patients were treated post-surgically by a 5-FU/pyrimidine protocol; only 3% of all patients received a cis-platinum-based therapy protocol. All pts suffering from a rectal carcinoma (n = 123) were additionally subjected to a radiotherapy protocol simultaneous with the 5-FU-based chemotherapy treatment.

At visit1, a total of 324 patients reported in an anamnesis interview about symptoms, which are the contributing factors to CRF, and, therefore justified the protocol-based trial enrollment diagnosis for CRF. The patients were further evaluated for supportive care treatment (ISC®Qu) during the postsurgical treatment period. 181 pts were enrolled into the supportive care group, 143 pts in the control group. For visit2 & 3 the forward or backward progress notes from the retrospective review charts were transferred into clinical research files and the CRF data were statistically assessed for an increase or decrease of individually diagnosed CRF during the postsurgical adjuvant chemo- or radio-chemotherapy period.

Statistical Methods

For statistical analysis the data subsets of the supportive care group and the control group with respect to the documented diagnosis and progress notes (v1 to v3) documented in the clinical research files were evaluated by the bimodal (binary, nominal) physician´s "yes" or "no" decision mode. A stratified multivariable-adjusted analysis for potential confounders and their impact on CRF was carried out with the multivariable logistic regression in order to minimize a possible confounder bias. The binary outcomes of the CRF diagnosis were weighted by confounder-adjusted odds ratios (Mantel-Haenszel baseline adjusted) and graphically displayed in forest plots.

Supportive Care Treatment

The supportive care treatment was carried out with commercially available batches of Iscador®Qu (ISC®Qu) provided by WELEDA, Arlesheim, Switzerland. A water-soluble injectable extract preparation was given subcutaneously at a total average dosage of 16.0 mg to 20.0 mg mistletoe extract per week. The daily splitting of the dosage within one week and the time of application within the weekly period were left with the physician´s discretion. There was a protocol-based mandatory demand to apply the indicated dosage range of Iscador®Qu extract (16.0mg to 20.0mg) per week. Iscador® 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 (Q = Quercus). One and two years old mistletoe leaves, stems and berries are harvested in summer and winter. The fresh plant is fermented with special starter cultures (*lactobacilli B18*) and the aqueous extracts are then blended on a complex machine. Through this special blending method the typical composition and quality of ISC®Qu is formed. The drug substance 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 pharmacological activities, the typical proteins (mistletoe lectins and viscotoxins) are routinely determined [8, 9].

RESULTS

Fig. (**1**) shows the number of patients identified with CRF at the time of the primary cancer diagnosis or at the time of the surgery of the primary (v1). Visit2 & visit 3 were commenced as indicated. The evaluation of the clinical research files, obtained from the general patients´ records allowed at visit1 to enroll 181 patients in the supportive care group and 143 patients in the control group. At the end of the adjuvant chemo- or chemo-radiotherapy regimen (v3), the number of patients in the supportive care group who initially reported symptoms of CRF dropped from 181 pts to 16 pts. In the control group, 86 pts out of 143 were still diagnosed with CRF. The multivariable-adjusted odds ratio (OR) for the supportive care versus the control group concomitantly demonstrates that the medical ISC®Qu preparation is likely to be a successful pharmacological intervention for the treatment of CRF, when ISC®Qu becomes an integral part of a chemo- or chemo-radiotherapy regimen in non-metastatic colorectal cancer patients.

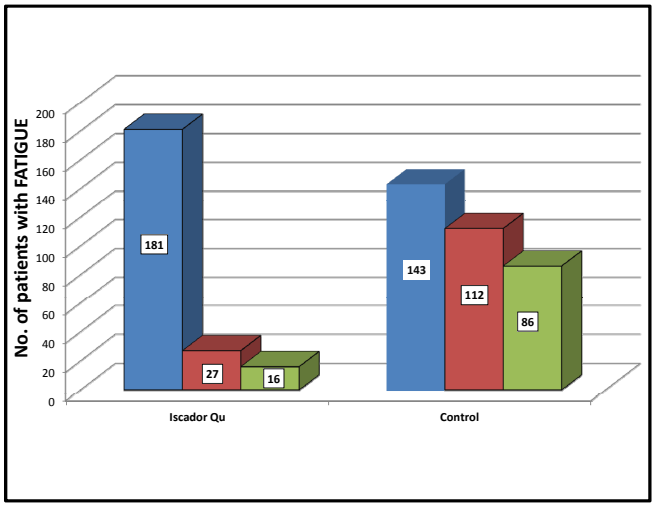


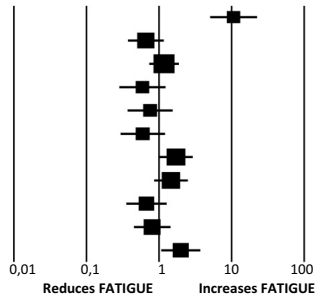
Fig. (1). The columns depict the number of patients diagnosed with symptoms of cancer-related fatigue at the time of diagnosis or surgical intervention (blue), in the midst of the chemo- or radio-chemotherapy protocol with and without ISC®Qu (green) and at the end of the chemo- or radio-chemotherapy with and without ISC®Qu (red). The left three columns present the data of the supportive care group (ISC®Qu), the right three columns the control group (without ISC®Qu).

The evaluation of the anamnesis interviews of 324 at v1 revealed that a significant number of tumor patients had already been suffered from CRF before their tumor was diagnosed or the primary was treated by surgical intervention. Therefore, it was possible to calculate an OR (10.651) for the supportive care intervention group (chemo- or radiotherapy with ISC®-Qu) and the control group (chemo- or radiotherapy) at v1. This OR estimates a 10-fold chance that at v1 there are more patients with fatigue in the supportive care intervention group than in the control group. Thereafter, the odds of both groups for the estimated chance to suffer from fatigue when treated and undergoing chemo- or radio-chemotherapy with or without ISC®Qu where calculated at v2 & v3. A significant (p = 0.001) reduction of the estimated chance (p = 0.001) suffering from CRF during treatment with the adjuvant chemo- or chemo-radiotherapy supported by ISC®Qu (OR = 0.047) is already achieved at v2 after 2.8 months (median duration period of adjuvant chemotherapy) and 4.3 months (median duration period of adjuvant radio-chemotherapy). The significantly (p = 0.001) decreased estimated chance (OR = 0.054) to suffer from CRF was kept constant until the end of the ISC®Qu supported therapeutic regimen (v3). V3 determined a period investigated of 5.2 months (median duration period of adjuvant chemotherapy) or a period investigated for 8.6 months (median duration period of adjuvant radio-chemotherapy). Forest plots over time beginning at v1, and extended to v2 & v3 were constructed to compare the CRF - ORs for 14 confounding factors concerning their independent impact and relative risk assessment for CRF (Fig. **2a-c**). From a patient care perspective these forest plots of adjusted CRF - ORs and their CIs are informative for all health care people involved in cancer treatment. It was found at v3, that the allocation of treatment (hospital versus practice, OR 0.354, CI 0.181-0.693, p = 0.002) influences significantly the outcome of CRF symptoms. In addition, the analysis of co-morbidity and CRF at v3 demonstrated a strong link, which is modulated by ISC®Qu from v1 to v3 (OR 0.574, CI 0.311-1.061, p = 0.076) in favor of decreased CRF. Co-morbidity/inflammation is an independent predictor for CRF and can therefore be successfully targeted by supportive care treatment within an adjuvant chemo- and radio-chemotherapy protocols in CRC patients. ISC®Qu is a putative candidate to be included in the standard protocols for the improvement of CRF (OR 0.054, CI 0.022-0.133 p = 0.001) as evidenced by the chronologically shown forest plots (Fig. **2a-c**), because the calculated confounder adjusted CRF - ORs of the supportive care treatment group are falling into the field in favor for ISC®Qu (decrease of fatigue).

DISCUSSION

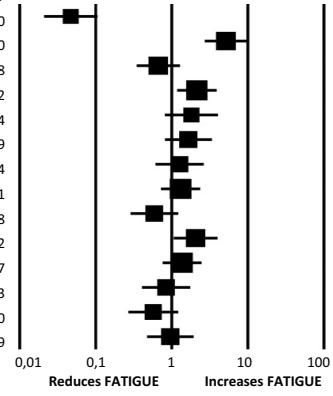
This study of colorectal cancer patients, - R0-resected, UICC stage I, II and stage III - investigated the clinical and unidirectional cause-effect relation of CRF, when post-surgical adjuvant chemo- or radio-chemotherapy protocols were applied. Analysis of the reported data was derived from the patients´ perception and the physicians´ diagnosis of CRF. The patients received adjuvant therapy schemes post-operatively, mainly based on 5-FU-leucovorin (patients with colon tumors) alone or post-operative local radiation plus

Criterion (variables)	Comparison	Time point	Statistics for each study					Odds ratio and 95% CI
			Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Iscador Qu therapy	YES vs. NO	before thearpy	10,651	5,093	22,276	6,284	0,000	
Center group	hospital vs. practice	before thearpy	0,659	0,375	1,157	-1,452	0,146	
Gender	male vs. female	before thearpy	1,173	0,737	1,866	0,673	0,501	
Age group	> 68 vs. <53 y.	before thearpy	0,592	0,286	1,225	-1,413	0, 158	
Age group	53-60 vs. <53y.	before thearpy	0,754	0,371	1,531	-0,782	0,434	
Age group	61-68 vs. <53y.	before thearpy	0,598	0,298	1,201	-1,445	0,148	
Comorbidity	YES vs. NO	before thearpy	1,721	1,023	2,895	2,046	0,041	
Tumor localization	rectum vs. colon	before thearpy	1,463	0,862	2,483	1,410	0,159	
Tumor grade	pD1-2 vs. pG3-4	before thearpy	0,672	0,357	1,266	-1,229	0,219	
Tumor UICC stage	II vs. I	before thearpy	0,805	0,454	1,428	-0,742	0, 458	
Tumor UICC stage	III vs. I	before thearpy	1,997	1,082	3,686	2, 211	0, 027	



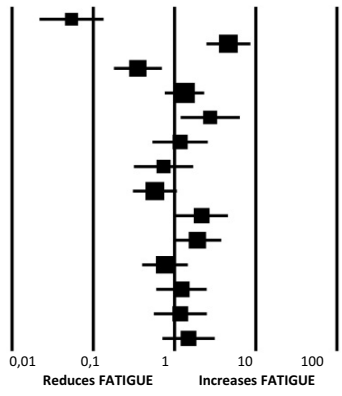
(a)

Criterion (variables)	Comparison	Time point	Statistics for each study					Odds ratio and 95% CI
			Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Iscador Qu therapy	YES vs. NO	after 1st cycle	0,047	0,021	0,105	-7,492	0,000	
Fatigue at baseline	YES vs. NO	after 1st cycle	5,151	2,272	9,730	5,051	0,000	
Center group	hospital vs. pracitce	after 1st cycle	0,665	0,347	1,273	-1,231	0,218	
Gender	male vs. female	after 1st cycle	2,135	1,184	3,849	2,522	0,012	
Age group	>68 vs. <53 y.	after 1st cycle	1,812	0,816	4, 025	1,460	0,144	
Age group	53-60 vs. <53 y.	after 1st cycle	1,654	0,821	3,333	1,408	0,159	
Age group	61-68 vs. <53 y.	after 1st cycle	1,266	0,613	2,614	0,638	0,524	
Comorbidity	YES vs. NO	after 1st cycle	1,307	0,727	2,351	0,894	0,371	
Radiotherapy	YES vs. NO	after 1st cycle	0,590	0,289	1,205	-1,448	0,148	
Chemotherapy	YES vs. NO	after 1st cycle	2,055	1,065	3,965	2,148	0,032	
Tumor localization	rectum vs. colon	after 1st cycle	1,363	0,762	1,439	1,043	0,297	
Tumor grade	pG1-2 vs. pG3-4	after 1st cycle	0,843	0,409	1,736	-0,463	0,643	
Tumor UICC stage	II vs. I	after 1st cycle	0,570	0,270	1,203	-1, 475	0,140	
Tumor UICC stage	II vs. I	after 1st cycle	0,956	0,476	1,919	-0,127	0,899	



(b)

Criterion (variables)	Comparison	Time point	Statistics for each study					Odds ratio and 95% CI
			Odds ratio	Lower limit	Upper limit	Z-Value	p-Value	
Iscador Qu therapy	YES vs. NO	end of therapy	0,054	0,022	0,133	-6,359	0,000	
Fatigue at baseline	YES vs. NO	end of therapy	4,600	2,486	8,510	4,862	0,000	
Center group	hospital vs. pracitce	end of therapy	0,354	0,181	0,693	-3,032	0,002	
Gender	male vs. female	end of therapy	1,323	0,763	2,294	0,997	0,319	
Age group	>68 vs. <53 y.	end of therapy	2,749	1,195	6,323	2,379	0,017	
Age group	53-60 vs. <53 y.	end of therapy	1,174	0,540	2,552	0,405	0,685	
Age group	61-68 vs. <53 y.	end of therapy	0,734	0,319	1,690	-0,727	0,468	
Comorbidity	YES vs. NO	end of therapy	0,574	1,311	1,061	-1,772	0,076	
Radiotherapy	YES vs. NO	end of therapy	2,157	1,030	4,518	2,038	0,042	
Chemotherapy	YES vs. NO	end of therapy	1,913	0,982	3,727	1,906	0,057	
Tumor localization	rectum vs. colon	end of therapy	0,764	0,403	1,449	-0,824	0,410	
Tumor grade	pG1-2 vs. pG3-4	end of therapy	1,218	0,600	2,472	0,546	0,585	
Tumor UICC stage	II vs. I	end of therapy	1,179	0,562	2,475	0,435	0,663	
Tumor UICC stage	II vs. I	end of therapy	1,488	0,714	3,101	1,061	0,289	



(c)

Fig. (2). (**a**-**c**): The statistical results of the adjusted odds ratios and their visualization in forest plots confirm the significant improvement of CRF in ISC®Qu supportively treated patients in comparison with the control group. The forest plots show the importance for the CRF prevalence of some confounders in course of the adjuvant therapy at visits 1, (**a**), visit 2 (**b**) & visit 3 (**c**). Among the potential confounders, comorbidity and the location of treatment (hospital *vs* private practice) appear important and suggest an independent influence on the outcome of CRF in CRC, who are post-surgically treated with adjuvant chemo- or radio-chemotherapy, supported by ISC®Qu.

5-FU (patients with rectal tumors); the observation period ended before 2008, when altered adjuvant regimens were recommended by new guidelines. Patients treated additionally in a supportive care intension with a pharmaceutical mistletoe preparation were compared with patients who received only the adjuvant chemo- or radio-chemotherapy. Using qualitative research methods and content analysis, the written statements (structured interviews for CRF) related to the impact of CRF were coded including the themes i) patients´ perception of CRF, ii) causes, iii) relief, iv) related symptoms/e.g. inflammation, v) meaning and vi) suffering. While expert guidelines now recommend regular screening for CRF, the conditions of CRF, because of its multidimensionality, remain consistently under reported and CRF often goes untreated [10]. Physicians may have insufficient knowledge about fatigue, its impact on HRQoL, while patients may consider it an unavoidable side effect that may incite a change toward less aggressive and therefore less effective cancer treatment [11]. Indeed many different terms are used to describe "fatigue" and it is unclear whether these word descriptors represent the same individualized cancer symptom or dimension. There is still a lack in etiology, definition and tools for measurement, but also in models to guide a clinical study of CRF, e.g. by selecting appropriate biomarkers, e.g. for persistent inflammation, and to set up the design of interventions [12].

Conventional cancer therapies might make patient sick. Supportive therapies that are now available to clinicians allow them to successfully control nausea, emesis and pain. However, this is not the case for CRF [13]. This retrospective data assessment from a cohort of fatigue diagnosed 324 patients presented here provides a framework of the intensity and temporal features of cancer- and therapy-related symptoms which can be alleviate by supportive care intervention with a medical mistletoe medication when concomitantly applied with a standard adjuvant chemo- or chemo-radiotherapy regimen. The symptom clusters of CRF during the course of cancer therapy often impair HRQoL and limits therapy options or effective dosage application. Inflammation may underlie CRF as recently shown in a study, which determined correlation coefficients between the fatigue dimensions and inflammatory markers [14].

Since decades, Viscum album preparations have been used in Europe in oncology. They show multi-facetted anti-tumor in-vitro activities, which include inhibition of tumor cell proliferation, induction of apoptosis, inhibition of angiogenesis, modulation of immune competence and gene signature expression [15]. Recently, it was demonstrated in-vitro that viscum album (ISC®Qu) exerts an anti-inflammatory effect, mostly directed to chronic inflammation by selectively inhibiting cytokine-induced expression of cyclooxygenase-2 [16]. A recent study found an association of CRF with increased plasma protein levels for serum amyloid A, collectin, and subunits of immunoglobulin G and complement C1q in disease-free breast cancer patients [17]. The authors conclude that CRF may be precipitated and prolonged by a non-specific sustained inflammatory response. The experimental data indicate [16] that ISC®Qu is a potential anti-inflammatory medicinal plant, and this efficacy - as derived from the molecular mode of action [16] - may contribute to the down modulation of presumed prolonged chaotic immune and inflammatory responses and therefore alleviate CRF. The results of a randomized, double-blinded trial, N07C2, with another herbal medication, the Wisconsin Ginseng versus a placebo in cancer survivors also demonstrated a benefit of American ginseng to improve CRF when taking daily 2000mg over a 8-week period [18]. Neither the American ginseng nor the medical mistletoe application showed discernable toxicities associated with the supportive care treatment. The data for ISC®Qu interpreted from the forest plots suggest a benefit of this supportive care medication as an effective intervention to improve CRF. The efficacy could be demonstrated for a median therapy treatment of 5.2 months during adjuvant chemotherapy alone (colon cancer patients.) and during a median treatment period of 8.6 months in a combined adjuvant chemo- and radiotherapy protocol (rectal cancer patients). It is interesting to note that patients who were treated supportively for CRF in the course of their disease in hospitals show a better outcome in respect to CRF compared to patients treated by office-based physicians. This data might probably reflect the fact that cancer patients visit more likely hospital clinics with the hope to get more clinically proven anti-cancer and therefore effective, but also more toxic treatment. This competence might include the skills of the doctors and nurses working in hospitals, which are not anticipated in office settings [19]. Interestingly, we learned from this study, that patients who were very sick were preferred candidates to get supportive care with ISC®Qu during the post-operative adjuvant chemo- or chemo-radiotherapy.

Understanding the characteristics associated to CRF may help the clinicians to identify patients at high risk for CRF associated with poor HRQoL and to plan medical and psychological or social interventions to improve the patient´s well-being early within the course of cancer treatment.

This study also demonstrates that co-morbidity is associated with an increased risk for suffering from CRF. Therefore it should be obligatory to identify patients in need of additional attention during the standard anti-cancer treatment to avoid or decrease CRF as a prevalent, distressing, and activity-limiting symptom.

Cancer is statistically seen a disease of the elderly and it is estimated that up to 70% of elderly with cancer experience CRF. The relationship between ageing process and pathogenesis of CRF is not fully understood. However, the results of a recently performed literature survey proposes an early diagnosis of CRF in the geriatric cancer population, along with its co-existing causes and co-morbidities [20], in order to select early in the course of the disease suitable clinical targets for interventions to improve CRF symptoms. A Norwegian breast cancer study examined the fatigue levels during the first year after chemo- or radiotherapy and hormonal therapy. They found that co-morbidity was significantly associated with increased levels of fatigue, interestingly, independent from other factors when e.g. compared to the general population; however, they concluded that co-morbidity seems to be a more important determinant for fatigue levels than the cancer treatment [21]. Therefore, all patients presenting with significant CRF should be evaluated for treatable conditions that might contribute to CRF. The Norwegian study and the present study concomitantly provide sufficient evidence that co-

morbidity might exhibit a casual association with CRF and therefore provide a potential target for interventions. Our study also confirms the recently published clinical results demonstrating that a systematic monitoring and treatment of physical symptoms are effective in alleviating CRF [22]. Furthermore, a first interim analysis from 220 patients with locally advanced or metastatic cancer of the pancreas who were solely treated with Viscum album (L.) (ISC®Qu) showed a significant and clinically relevant prolongation of overall survival as well as less disease-related symptoms with limitation in HRQoL than a control group, receiving no anti-neoplastic therapy [23].

In breast cancer patients there were substantial genetic findings that increased activity of pro-inflammation-related genes in leucocytes may contribute to persistent CRF [24]. Furthermore, single nucleotide polymorphism in the promoter region of the cytokines ILB -511 C>T (rs 16944), IL6 -174 G>C (rs1800795) and TNF -308 G>A (rs 1800629) suggests an inflammatory basis for fatigue [25]. Already in 2007, Bower JE [26] summarized emerging evidence that inflammatory processes my be involved in CRF during and after treatment and his group recently examined the hypothesis that CRF is driven by activation of the pro-inflammatory cytokine network [27]. The hypothesis driven view that CRF is related to inflammatory processes [28] or to the serotonin, to the vagal-afferent activation, to the anemia and to the adenosine triphosphate hypotheses [29] has a history since midth of 2007. A small proof of concept study by Kamath J (2012) administrating thyrotropin-releasing hormone in cancer survivors was associated with significant improvement of CRF and decreased C-reactive protein levels, a marker for inflammation [30]. The results of an attractive clinical study focusing on epigenetic changes of DNA methylation patterns in isolated PBMCs from breast cancer patients was reported by the group of Smith AK *et al*. [31]. They suggested that persisting epigenetic changes secondary to chemotherapy may be one factor that contributes to inflammation and its consequences including CRF in vulnerable breast cancer patients.

Our retrospective study revealed that CRF might already exist prior to cancer diagnosis. CRF prior to the onset of cancer treatment is a strong predictor of persistent fatigue [32]. Therefore, perception of the syndrome of CRF has a high priority for many cancer patients, especially the elderly. The findings that inflammatory processes may contribute to CRF suggest a mechanism-driven intervention for vulnerable patients at risk using anti-inflammatory allopathic [33] drugs and/or clinically proven herbal medicine [34]. Anti-inflammatory agents that can modulate the NF-kappa B activation and inflammatory pathways may also have a potential to improve CRF in tumor patients, also, because of their multi-targeting properties, low cost, low toxicity and immediate availability [35]. Very recently, it was shown noticeably that an Iyengar yoga intervention specifically designed for fatigued breast cancer survivors would lead to decrease in inflammation-related gene expression and circulating markers for pro-inflammatory cytokine activity [36]. Data from a transcriptome analysis using a whole human genome chip (Agilent) approach and four different breast cancer cell lines already pointed out that different Iscador® preparations selectively influence in-vitro gene-expression patterns concerning pro- and anti-inflammatory responses [37].

This retrospective assessment of CRF in colorectal cancer patients., the emerging evidences that inflammatory processes may be involved in CRF and the first targeted interventions to treat the onset or persistence of inflammation successfully, form a platform for further experimental studies and controlled prospective clinical trials to improve CRF and quality of life in cancer patients.

CONCLUSION

The pre-clinical [15] and clinical results [6, 7, 22] and the mode of action with special reference to cope with chronic anti-inflammatory processes provide a scientific and clinical rationale to use ISC®Qu medication within chemo- and chemo-radiotherapy protocols in CRC patients with the intention to deliver supportive care treatment which decreases CRF symptoms and improves HRQoL.

CONTRIBUTIONS

JH and PRB commenced the retrospective clinical trial and did the statistical work. HM was mainly responsible to provide the patients´ clinical records. KSZ is supported by the Fritz-Bender-Foundation, Munich, and framed the data to a medical working hypothesis and wrote the manuscript.

CONFLICT OF INTEREST

JH and PRB received a research grant from HISCIA, Foundation for Cancer Research Arlesheim, Arlesheim Switzerland. HM and KSZ declare that they have no competing interests. The authors alone are responsible for the content and writing of the manuscript. With this statement all authors mentioned in this study disclosed that there are no financial or personal relationship with other people or organizations that could inappropriately influence the work.

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