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A Controlled Study of a Lecithinized Delivery System of Curcumin (Meriva®) to Alleviate the Adverse Effects of Cancer Treatment

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A proprietary lecithin delivery system of curcumin (Meriva) was evaluated in a controlled study to assess its efficacy in alleviating the side effects of cancer chemo- and radiotherapy in 160 patients undergoing these treatments. In both cases, a semi-quantitative evaluation of the side effects was carried out using a visual analogue scale, assessing also the plasma free radical status in all patients. Results showed that lecithinized curcumin might alleviate the burden of side effects associated to chemo- and radiotherapy, suggesting that the anecdotal use of various preparations of curcumin as a supportive agent for cancer treatment is well worth a systematic investigation in larger scale clinical trials. The capacity of curcumin to upregulate anti-oxidative responses and downregulate inflammatory pathways could explain its beneficial effect in tempering the prolonged and systemic oxidative and inflammatory effects of cancer treatment, and the beneficial effects observed in the plasma oxidative status in all patients of the treatment group support this view. © 2013 The Authors. Phytotherapy Research published by John Wiley & Sons, Ltd.

Keywords: curcumin; Meriva; supportive care; cancer; chemotherapy; radiotherapy.

INTRODUCTION

Despite the development of new therapies, cancer remains the second leading cause of death after cardiovascular disease in Western countries, accounting for nearly one in every four deaths, with 569,490 Americans being estimated to die of cancer in 2010 (American Cancer Society 2010). Since medical innovation does not follow Moore's law, the cost of cancer treatment is also skyrocketing (Sullivan *et al*., 2011). In industrial countries, this is expected to exacerbate the gap between the increasing therapeutic needs of an aging society and the decrease in its health resources imposed by the demographic trend. Curing cancer is, undoubtedly, a challenging task, and gets the lion's share of media attention and government funding for oncologic research (Gullett *et al*., 2010). Conversely, chemoprevention, which maintains the status quo of good health, and supportive care, which improves the quality of life of cancer patients, are perceived as less glamorous and challenging. Because of these skewed priorities, the vast bulk of cancer research is therapeutically oriented, and chemoprevention and supportive care are still often perceived with skepticism, as if cancer were unavoidable and the quality of life of cancer patients hopelessly poor.

Due to a combination of long-term safety and a pleiotropic mechanism of action, dietary natural products are considered prime candidate for chemoprevention, since they show an excellent profile of side effects and are capable to cope with the mechanistic redundancy involved in the development of cancer (Gullett *et al*., 2010). The same reasons also qualify them as potentially useful for supportive care, since the non-surgical treatment of cancer (chemo- and radiotherapy) is characterized by an overexpression of pathways involved in inflammation and in the generation of ROS, a condition difficult to manage with single specific agents (Gullett *et al*., 2010). Within chemopreventive dietary compounds, the preclinical validation of curcumin, the diarylheptanoid yellow dye of turmeric, is nowadays consolidated and widely accepted. Curcumin can inhibit carcinogenesis at the initiation, promotion, and progression stages (Steward and Gescher, 2008), and its multimodal action is mediated by the block of signal transduction pathways associated to the development of cancer. The hallmark of curcumin is the functional and genomic inhibition of enzymes generating ROS and inflammatory lipids (COX, LO, xanthine oxidase, NOs), of pro-inflammatory transcription factors (NF-kB, STAT3) and kinases (PKC, EGFR tyrosine kinase), as well as the upregulation of anti-oxidant pathways via activation of Nrf2 (Steward and Gescher, 2008).

Although very ambitious and promising, the development of curcumin as a chemopreventive agent is still in

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its infancy (Steward and Gescher, 2008), and its study as an anti-cancer agent has not yet progressed from animal models (Guo *et al*., 2012; Lin *et al*., 2012; Sharma *et al*., 2011; Yamauchi *et al*., 2012). On the other hand, curcumin has also shown promising activity in various preclinical models of cancer supportive care (Siddiqui *et al*., 2009), suggesting that this compound could have a significant impact on therapeutic compliance, reduction of adverse events, and quality of life in cancer patients.

One major problem with curcumin, especially marked in a supportive care context, is its dismally low oral bioavailability, especially from non-dietary pharmaceutical matrixes, with the need to administer mega-dosages (up to 8 grams) of this compound to patients with often already altered taste perception, difficulties to swallow, and intestinal disturbances (Dhillon *et al*., 2008). In this context, the development of improved formulations of curcumin could have a dramatic effect on compliance, making it possible to systematically assess the clinical value of this compound in cancer supportive care. To this purpose, we have used a proprietary lecithinized formulation of curcumin (Meriva) to investigate, in a controlled study, the potential of curcumin on the quality of life in a population of 160 cancer patients undergoing chemo- or radiotherapy following surgical treatment. In a previous human pharmacokinetic study, Meriva has been shown to dramatically improve the absorption of curcumin (Cuomo *et al*., 2011), effectively solving the issue of megadoses that had plagued the clinical research on this dietary constituent and paving the way to the clinical translation of its promising biochemical and preclinical potential.

STUDY DESIGN

Patients

General inclusion/exclusion criteria. Surgery had been performed at least 1 month before this study period. Hepatic and renal functions were within normal values. All patients were considered in reasonably good conditions, with a score ≥70% on the Karnofsky scale (Table 1). No infections, metabolic, or clinical conditions were present. There was no other medical treatment. Only patients with clinically significant side effects following oncological treatments were included. As a further inclusion criterion, plasma oxidative stress (FRAS system (Finco *et al*., 2012) was increased in all patients enrolled in this study.

Chemotherapy patients. Patients under treatment for solid tumours [colon/rectum (34%), liver or kidney (12%), stomach (11%), lung (23%), female genital system including the ovaries (11%)], or haematological malignancies (9%) were enrolled. In 35% of these patients, there was more than one localization of the main tumour, but terminal patients were excluded, and most subjects were in relatively good conditions (both physical and psychological), with a score ≥70% on the Karnofsky scale of health (Table 1) (Schag *et al*., 1984). For all patients, chemotherapy had started at least 1 month after surgery or interventional procedures (removal of the main tumours or reduction of tumour mass), from which they had already recovered. There were no detectable metastases in 65% of patients, and all patients were chemotherapy naives. No infections or severe blood test alterations were present at inclusion into the follow-up evaluation period, nor were diabetes and major metabolic or cardiovascular disorders that required a specific treatment. The chemotherapy regime of the patients was based on 5-fluorouracil (5FU) alone (colon/rectum, liver, and gastric cancers) or in combination with cisplatin (genitourinary cancers), vinblastine and CCNU (kidney cancer), cisplatin and gemicitabine (lung cancer), or MOPP/ABVD/COPP schedules (haematological malignancies). Due to the preliminary nature and the small size of this study, no attempts were done to correlate responses to a specific therapeutic schedule or pattern of side effects.

Table 1. The Karnofsky Scale as developed by Karnofsky, Abelmann, Craver, and Burchenal (1948). The 100-point Karnosky scale allows to rapidly screen the condition of patients on a given day, without going through several, complex multiple-choice questions or sign/symptoms surveys more demanding for patients and staff

Included into this study:	
100	Able to work. Normal: no complaints: no evidence of disease.
90	Able to work. Able to carry on normal activity; minor symptoms.
80	Able to work. Normal activity with effort; some symptoms.
70	Independent; not able to work. Cares for self; unable to carry on normal activity.
Excluded from this study:	
60	Disabled; dependent. Requires occasional assistance; cares for most needs.
50	Moderately disabled; dependent. Requires considerable assistance and frequent care.
40	Severely disabled; dependent. Requires special care and assistance.
30	Severely disabled. Hospitalized, death not imminent.
20	Very sick. Active supportive treatment needed.
10	Moribund. Fatal processes are rapidly progressing

Radiotherapy patients. Patients were under treatment for solid tumours involving the colon/rectum, liver or kidney, stomach, or lungs. More than one tumour localization was present in 3/4 of these patients, and terminal patients were excluded from the study. Most patients were in reasonably good conditions, with a score ≥70% on the Karnofsky scale (Table 1). Radiotherapy had started at least 1 month after surgery or interventional procedures (surgical removal of the main tumours or reduction of tumour mass), and patients had fully recovered before the beginning of the study. There were no detectable metastases in 78.4% of the patients, who were all radiotherapy-naives. The presence of infections or of severe blood test alterations was an exclusion criterion. Patients with metabolic or cardiovascular disorders requiring treatment were, likewise, excluded. The total dose of radiation applied ranged from 30 to 50 Gy with conventional fractionation (1.8-2.0 Gy/day) administered with Linear Accelerator machine, 6-10 MV photon beam energy and with conformal three-dimensional techniques (3D-CRT).

Evaluation incidence and severity of the side effects

The assessment of the incidence of side effects was recorded by means of a diary that patients kept over the duration of the study. The investigational period started immediately after patients had completed their first cycle of chemo- or radiotherapy, whose duration ranged between 10 days and 1 month, and lasted for 2 consecutive months from this date, irrespective of the total duration of the therapy. The side effect recorded was judged relevant for the incidence assessment when they fulfilled one of the following criteria:

- Duration longer than three days.
- Requirement of medical attention.
- Requirement of medical treatment or hospitalization, irrelevant of the duration.
- Inability of patients to work or participate to social activities.

More transient, less severe side effects were not considered relevant for the analysis of the incidence of side effects. The severity of individual side effects was judged semi-quantitatively using an analogue scale responding with values ranging from '0' (absence of side effects) to '5' (side effect requiring medical attention), or up to '10' (very severe side effect requiring immediate hospital admission). The score (on an analogue line) was assigned by the patients with the help of the physician on the basis of the diary and on clinical, biomedical, and laboratory values (i.e. for cardiotoxicity, hepatotoxicity, nephrotoxicity, and ototoxicity). Just like palliative care, also cancer supportive care research relies extensively on descriptive end-points (Schag *et al.*, 1984), and the analogue scale criteria used in this study are presented in Table 2.

Patients were evaluated in the clinic at trial inclusion after completion of the first chemo- or radiotherapy cycle and again after two months, with phone or personal contacts every two weeks.

Table 2. Scores in the analogue scale employed to judge, in a semi-quantitative way, the severity of individual side effects in radio- or chemotherapy patients (Dugall, Hosoi, Belcaro)

Explanation of the score:
0. No effects.
1. Localized subclinical side effects (i.e. initial oedema on standing).
2. Systemic, weak, subclinical side effects.
3. Subclinical side effects; laboratory values are altered.
4. Borderline/subclinical side effects: initial, significant signs/symptoms, and altered laboratory values.
5. Side effects requiring medical attention; clear signs/symptoms.
6. Symptomatic side effects requiring medical (drug) treatment and specialist advice.
7. Severe, multiple side effects requiring immediate medical attention; organ damage (limited or transient or functional only).
8. Severe, multiple side effects requiring immediate medical attention; organic organ damage and danger of failure.
9. Severe signs/symptoms (as in 8) with multiple, severely damaged organs.
10. Severe, multiple side effects endangering the life of the patient and requiring immediate hospital admission.

The presence of superficial vein thrombosis or deep vein thrombosis was detected (even in asymptomatic subjects) using ultrasound imaging performed by a trained angiologist or vascular surgeon. All patients were clinically examined, and the lower limbs were scanned in all patients at inclusion and again after 2 months. In case of any symptom suggesting a thrombosis, this was immediately evaluated clinically by ultrasound imaging. The ultrasound scanning was carried out according to methods described previously (Steigerwalt *et al.*, 2009).

Treatment and controls

The study was performed according to the Declaration of Helsinki, and all patients gave an informed consent prior to their participation to the study. Patients were given one tablet containing 500 mg Meriva (composed of 100 mg curcuminoids (ratio curcumin : demethoxycurcumin : bis-demethoxycurcumin 33 : 8 : 1), 200 mg soy lecithin and 200 mg microcrystalline cellulose, or a comparable tablet (defined below as a comparable blank formulation, devoid both of curcuminoids and soy lecithin) after each of the three major daily meals. Verum and comparable tablets had an identical appearance, size, and shape. The observational framework study lasted 4 months, starting from the day after their first cycle of chemotherapy of radiotherapy. Meriva was used between the 4^{th} and 16^{th} weeks from surgery, for at least 60 consecutive days.

Patients

Chemotherapy patients. 80 patients were enrolled, and 78 of them (age 35 to 70 years) completed the study. 40 Subjects (Group A, 20 males and 20 females; mean age 53.4 years $\pm$ 6.6) received, along with the 'best available medicine' also Meriva, while a control group 'best treatment' only and the comparable blank formulation (20 males and 18 females; mean age 50.2 years $\pm$ 7.2). Dropouts were the result of non-medical problems related to organizational and timing issues affecting treatment and/or follow-up schemes.

Radiotherapy patients. 80 patients (age 35 to 70 years) were enrolled. 40 patients (Group A, 18 males and 22 females; mean age 55.8 years $\pm$ 3.3) were treated with the 'best treatment' and Meriva, while the same number of patients (21 male and 19 women; mean age 53.7 years $\pm$ 4.3) was treated with the best treatment only and the comparable blank formulation. No dropouts were observed in either group.

Plasma free radical (PFR) status

The evaluation of oxidative stress was performed with a FRAS system (Corcon, Parma, IT) measuring the level of PFRs in a single drop of blood (from fingers), a method validated in previous studies (Finco *et al.*, 2012).

Table 3a. Incidence of symptoms and signs (percent of patients with side effects) resulting from chemotherapy as assessed by a diary recorded over a period of two months

	MERIVA (%)	CONTR (%)
Nausea and vomiting	40	68.7*
Diarrhoea or constipation	38	67*
Malnutrition/weight loss	28	36*
Memory or cognitive function alteration	22	35*
Infections/sepsis	18	32*
Neutropenia	28	46*
Platelet count	29	32
Cardiotoxicity°	22	31*
Hepatotoxicity	20	23
Nephrotoxicity	9	11
Ototoxicity	9	12
Medications required for side effects	58	77*

°Cardiac symptoms (i.e. arrhythmia, chest pain, hypotension, cardiac dilatation etc.) clinically related to chemotherapy

No fatal incidents occurred during the observational period.
* = $p < 0.05$ (comparison with control group).

Statistical analysis

In view of the exploratory character of our study, and the diversity of patient's malignancies and treatment regimen and dosages, the statistical analysis was made using non-parametric statistics, in accordance with the pilot nature of the trial, whose aim was to evaluate a beneficial effect on the side effects associated with cancer treatments. Study populations, statistics, and dosages were selected upon anecdotal data on the efficacy of Meriva to moderate the side effects of radio- or chemotherapy recorded over the past three years. An estimate of not less than 15 subjects completing the study in each group was considered as necessary to obtain clinically meaningful data on the treatment outcomes (Belcaro *et al.*, 2008). The control population was composed by the subjects recruited into the study who received their standard chemo- or radiotherapic treatment schedule without the addition of Meriva. The intention-to-treat (ITT) efficacy analysis included all the subjects who received at least one dose of medication and had at least one post baseline measurement of the primary efficacy items. Subjects having treatment compliance <70% were excluded.

The ITT analysis was performed comparing 'all treated subjects' versus control subjects. The per-protocol (PP) analysis should have included all subjects available for the ITT analysis, who completed the planned duration of treatment, were compliant to the regimen, had a valid efficacy evaluation, and did not violate the protocol in any way liable to influence the efficacy outcome. A range of compliance of >70% was adopted as a criterion to select subjects for the PP analysis. Therefore, subjects with compliance below 70% were excluded, as well as all the subjects who did not meet the criteria for the 'Population for efficacy analysis'.

Additional ('post-hoc') analysis was made assessing the minimum effective time 'dose' to reach significant results. These tests were performed using closed testing procedures. The fixed sequence Dunnett test was applied to determine the time needed to have results on each, specific collateral effect. All hypothesis tests were two sided. All statistical tests (non-parametric) were performed at a 5% significance level ($p < 0.05$, Mann–Whitney test through Sigma-Plot computer software).

RESULTS

Evaluation of side effects

Chemotherapy:. The incidence of symptoms and signs (percent of patients with side effects) resulting from chemotherapy as assessed by a diary recorded over a period of two months is shown in Table 3a. The incidence of signs/symptoms observed and described by patients and confirmed by the caring health operator was significantly lower in the Meriva group (namely a decreased percentage of patients described the sign/symptom) ($p < 0.05$). Table 3b shows the semi-quantitative evaluation of side effects with an analogue scale. There were significantly lower values (scores) in the Meriva treatment group ($p < 0.05$) in comparison with controls. No significant changes (excluding memory and cognitive function or impairment) in scores were observed in the control patients.

The PFR status was increased in both groups at the inclusion (PFR >450 Carr units with an average of 467 ± 29 in Meriva patients and 471 ± 18 in controls). A decrease to an average value of 389 ± 33 Carr units was observed in the Meriva patients versus an increase to 478 ± 39 Carr units in the control patients (intergroup difference: $p < 0.022$). The difference before and after the treatment with Meriva in the treated group was statistically significant ($p < 0.021$).

Table 3b. Semi-quantitative evaluation of cancer chemotherapy side effects by means of a visual analogue scale. Values are given for each group at inclusion (INC) subsequent to the first chemotherapy cycle over a period of 2 months of further chemotherapy. VAS values (mean) are presented together with standard deviation in brackets

	MERIVA		CONTR	
	INC	2 Mo	INC	2 Mo
Nausea and vomiting	6.6 ± 2.1	4.2 ± 2*	6.9 ± 2.2	7.1 ± 2.1
Diarrhoea/constipation	7.3 ± 1.8	3.6 ± 1.2*	7.3 ± 1.8	6.7 ± 2.2
Fatigue	8.2 ± 1	7 ± 2.1*	8.4 ± 1.1	8 ± 1.4
Malnutrition/weight loss	7.7 ± 1.2	4 ± 1.7*	7.9 ± 1.5	7.6 ± 1.6
Memory/cognitive function impairment	8.6 ± 2	5.4 ± 1.1*	8.4 ± 1.6	6 ± 1.9

* = $p < 0.05$ (comparison with control group).

Table 4a. Radiotherapy. The incidence of side effects recorded for patients during two months

	MERIVA (%)	CONTR (%)
Acute side effects		
Damage to epithelial surfaces (skin, mouth, pharyngeal and bowel mucosa, urothelium)	22	51*
Damage to mouth, throat, oesophagus, and bowel	19	24*
Soreness and ulceration in the mouth and throat	12	25*
Swallowing problems	11	22*
Sore oesophagus	19	24*
Diarrhoea and nausea	15	22*
Swellings/oedema of lower limbs	35	61*
Generalized fatigue	42	57*
Weakness	38	63*
Medications required for side effects	51	64*

*$p < 0.05$ (comparison with control group).

Radiotherapy. The comparative results for radiotherapy side effects (Table 4a) showed a significantly higher global percentage of patients experiencing signs/symptoms due to side effects ($p < 0.05$) in comparison with controls. The semi-quantitative evaluation of the reported side effects with an analogue scale is presented in Table 4b. Significantly lower values (scores) were observed in the Meriva treatment group ($p < 0.05$) in comparison with controls, where no significant variations in scores were observed.

The PFR status was increased in both groups at the inclusion stage (PFR >440 Carr units), with an average value of 471 ± 22 for Meriva patients and 465 ± 22 for the control. There was a decrease to an average of 382 ± 29 Carr units in Meriva patients, while an increase to 476 ± 42 Carr Units was observed in the control branch. The difference between the groups was statistically significant ($p < 0.022$), as was that in the Meriva branch before and after the treatment ($p < 0.021$).

Overall, Meriva did not cause any clinically significant side effect, and the tolerability was good, with no patients having to stop the administration. Compliance was also optimal (>97%).

DISCUSSION AND CONCLUSIONS

The side effects of radiotherapy and chemotherapy are often related in a predictable and specific way to the mechanism of action of the treatment (Harrington and Smith 2008). On the other hand, they also depend on a number of extremely diverse and interconnecting variables that include the presence/absence of residual tumours, infections, inflammation, haematocrit, and the basic status of the subjects (age, sex). Notwithstanding these issues, the release of active or necrotic elements, mainly tumour necrosis factor, and an increase in the plasma oxidative status are generalized in cancer patients under non-surgical treatment (Conklin 2004). Several attempts have tried to control oxidative stress in cancer patients, owing to its potential to improve the tolerability of chemo- and radiotherapy, but the issue of the potential complication with the management of the disease remains largely unsettled (D'Incalci *et al*., 2007).

The use of herbal ingredients in cancer patients is widespread and often goes unreported to clinicians (Deng and Cassileth 2005). Curcumin is probably the most popular herbal product within the cancer patients community, and the web is rife with ingenious recipes to formulate megadoses (>3 g) of this dye with fatty foods like olive oil or chocolate to overcome the issue of the low availability of the natural product. Curcumin has also been added to the mainstream treatment of myeloma patients, and its potential to increase the tolerability of certain anticancer drugs (docetaxel, 5FU) has given promising clinical results (Bayet-Robert *et al*., 2010). Nevertheless, no systematic study on the effect of the addition of curcumin to standard cancer treatments has been reported so far, and most of the glamour associated to curcumin as a cancer supportive agent relies on anecdotal reports, preclinical studies, and mechanistic considerations. The clinical translation of these studies has been hampered by the exceedingly low oral bioavailability of curcumin, which requires the administration of megadoses that defy compliance in many patients (Dhillon *et al*., 2008). To overcome this issue, we have focused on a lecithinized formulation of curcumin (Meriva) that shows an improved absorption compared to the natural product (ca. six fold on weight basis and 30-fold on molar basis) (Cuomo *et al*., 2011) and have investigated its potential to increase the tolerability of cancer treatment.

Table 4b. Semi-quantitative assessment of side effects resulting from cancer radiotherapy by means of a visual analogue scale. Values are given for each group at inclusion (INC) subsequent to the first radiotherapy and during a follow-up period of 2 months with further radiotherapy cycles. VAS values are presented mean and SD

	MERIVA		CONTR	
	INC	2 Mo	INC	2 Mo
Nausea and vomiting	5.5 ± 1.4	2 ± 1.1*	4.4 ± 1.2	4.5 ± 2
Diarrhoea/constipation	5.1 ± 1	2.3 ± 1.5*	4.7 ± 1.1	4.6 ± 1.7
Fatigue	8.8 ± 1.5	3.3 ± 0.6*	8.3 ± 1.1	8.4 ± 1.5
Malnutrition/weight loss	8.6 ± 1	6.3 ± 2*	8.8 ± 1.1	8.1 ± 0.6
Memory/cognitive function impairment	7.3 ± 0.8	4.2 ± 1*	7.7 ± 1.1	7.9 ± 1.2
Local pain/swellings at site of therapy	6 ± 2.2	2.7 ± 1.1*	6.4 ± 1	6.9 ± 1.8

*$p < 0.05$ (comparison with control group).

Curcumin behaves as a veritable master switch of inflammatory and anti-oxidant responses, inhibiting inflammatory enzymes and their expression, and upregulating anti-oxidant defences (Steward and Gescher, 2008). This broad mechanism of action suggests that curcumin could mitigate the inflammatory and oxidative phenotype associate to cancer treatment by both chemo- and radiotherapy. To this aim, a population of 160 cancer patients was enrolled in a pilot controlled trial where Meriva was added to the standard treatment required by the specific type of malignancy present. Patient-reported subjective measurements of symptoms were used as a primary end-point of the study. A symptoms scale that included a series of common side effects of cancer treatment at intestinal (diarrhoea/constipation), brain (nausea/vomiting, appetite loss, memory loss), and blood (decreased platelet and neutrophil count) level was used, monitoring also toxicity at specific organs (heart, liver, kidney, ears) and the overall use of medication to manage the side effects of the treatment. Curcumin has an excellent profile of tolerability in humans, and gastric and intestinal upset are the only major side effect documented with megadosages (>10 g/die) of the compound (Hsu and Cheng 2007). Based on human studies, it is generally recognized that curcumin does not cause significant short-term toxicity at dosages up to 8 g/day for four months. At the low dosages (300 mg curcumin as Meriva) used in the study, it seems therefore reasonable to assume that curcumin is essentially devoid of side effects, and that all the discomfort recorded in patients' diaries was related to the cancer treatment regime (chemo- or radiotherapy).

At the outset of the treatment, the quality of life of patients was acceptable, with a score on the Karnofsky scale of at least 70, as expected in chemo- and radiotherapy-naive patients soon after surgical treatment of their malignancy (Schag *et al*., 1984). A consistent improvement of the side-effect profile was observed in the treatment groups from both chemo- and radiotherapy. While some effects are clearly related to the anti-inflammatory and anti-oxidant profile of curcumin (reduction of gastrointestinal, cardio-, nephro-, and oto-toxicity as well as infection and malnutrition) and are backed up by solid preclinical documentation, other were less predictable (effect on alterations of cognitive function and neutropenia) and are worth mechanistic investigation.

The subjective end-points considered in this study were complemented by a biochemical end point (investigation of the plasma oxidative status). As expected from the anti-oxidant action of curcumin, the plasma oxidative status was consistently improved in all patients supplemented with Meriva. This observation might be related to the general improvement of the side-effect profile of the cancer treatment, but, due to the heterogeneity of the patients' population, no attempt was done to correlate the improvement in quality of life with that of the plasma oxidative status.

As a Pgp inhibitor, curcumin could, in principle, increase the bioavailability, and therefore both the activity and the side effects, of many chemotherapeutic drugs (Chearwae *et al*., 2004). The clinical relevance of this observation is, however, unclear and complicated by the observation that commercial curcumin is a mixture of three related curcuminoids with different inhibitory properties on PgP and sensitivity to the absorption-boosting effect of lecithin formulation (Cuomo *et al*., 2011). In fact, formulating with lecithin, a strategy inspired by the dietary use of turmeric in fatty matrixes like coconut milk or chocolate, increases the absorption of the minor curcuminoids (demethoxycurcumin and bis-demethoxycurcumin) much more than that of monomolecular curcumin, with demothoxycurcumin and not monomolecular curcumin being the major plasma curcuminoids with Meriva administration (Cuomo *et al*., 2011). Demethoxycurcumin, a more potent anti-inflammatory agent than curcumin in many assays (Cuomo *et al*., 2011), is a less potent PgP inhibitor (Chearwae *et al*., 2004), but bis-demethoxycurcumin is the most potent curcuminoid in terms of down-regulating the expression of the Pgp gene (Kaposztas *et al*., 2009; Limtrakul *et al*., 2004). Apart from gastro-intestinal upset associated to megadosages, interaction with the metabolization of xenobiotics is considered the major side effect associated to curcumin (Mancuso and Barone 2009). Because of the different potential for drug interaction of curcuminoids, and their different absorption from formulated and non-formulated matrixes, it is difficult to compare the potential for drug interaction of Meriva and unformulated curcumin.

This study is clearly limited by the heterogeneous nature of the patient cohort investigated in terms of age, sex, type of malignancy, and medication, by the generality of the side effects considered, and by the lack of a dose adjustment in relation to the treatment. It does not, obviously, provide any indication that curcumin can have a positive effect on the course of the disease, as claimed by anecdotal information popular within the cancer patients community, nor disprove the risk that curcumin, as an antioxidant, might interfere with cancer treatment. Nevertheless, it provides a first clinical evidence that this compound, when suitably formulated to overcome its poor oral absorption, can indeed have an interesting potential for lowering the burden of side effects associated to cancer therapy, with an overall improvement of the quality of life that might translate into a better compliance with the treatment and, potentially, into an overall improved survival rate.

Conflict of Interest

The author Stefano Togni is an employee of Indena SpA, who manufactures Meriva. The author Giovanni Appendino is chief scientific advisor to Indena SpA. No conflict of interest is reported for the other authors.

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