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ORIGINAL ARTICLE

Oral nutritional supplement prevents weight loss and reduces side effects in patients in advanced lung cancer chemotherapy

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Abstract

Weight loss in patients with cancer is caused by cancer cachexia and chemotherapy-induced nausea and vomiting. Recent developments in antiemetic drugs have substantially improved nausea and vomiting, but this intervention did not reduce weight loss and other more severe side effects of chemotherapy, like anorexia, weakness, cough, dyspnea, hemoptysis, and pain. This study aimed to investigate the effects of nutrition intervention with a food supplement, during chemotherapy in patients with advanced nonsquamous non-small cell lung cancer (NSCLC). Patients received individualized nutrition counseling by a registered dietitian and were provided with oral supplements of Texidrofolico® for 90 days. Bodyweight and the mentioned other side effects were evaluated at baseline and after 90 days of intervention. To assess the effects of this dietary supplement, a total of 30 patients were retrospectively enrolled as controls, and the bodyweight and change in side effects of chemotherapy were compared with those observed in 30 Texidrofolico®-treated patients. After 90-day intervention, by oral supplement of Texidrofolico®, the patients, during the course of cytotoxic chemotherapy, showed an improved quality of life and not significant weight and BMI loss respect the control group. Furthermore, the number of patients, treated with Texidrofolico® who maintained or increased their body weight, after 90 days of treatment was significantly higher than in the control group. The effects of treatment with the food supplement have also been studied from a metabolic point of view. It was possible to find that one of the known markers of tumor growth, plasma polyamines, was reduced after the treatment. A possible relationship between these biogenic amines and the folate cycle is discussed. In conclusion, early intensive nutrition intervention with oral supplements of Texidrofolico® during chemotherapy of NSCLC patients prevents weight loss and it is beneficial for their quality of life.

Keywords NSCLC · Chemotherapy · Polyamines · Nutritional supplement · Quality of life

Introduction

Lung cancer is one of the leading causes of cancer deaths (Wang et al. 2019). In particular, non-small cell lung cancer (NSCLC) is the most frequent of all lung cancers and is related to cigarette smoking (Liu et al. 2019). NSCLC is a tumor with aggressive malignancy, with poor patient prognosis and a very low survival rate (David et al. 2017). Conventional therapeutic treatment is based on treatment with various chemotherapeutic agents such as Pemetrexed®, cisplatin, carboplatin, etoposide, irinotecan, topotecan, doxorubicin, adriamycin, or cyclophosphamide (Kang et al. 2016). However, resistance to the drugs mentioned is frequent, which makes chemotherapy ineffective. Pemetrexed® (LY231514, Alimta; Eli Lilly and Company, Indianapolis, IN) is an antifolate that is metabolized intracellularly in

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a form of pentaglutamate**.** It is used to treat patients with unresectable malignant pleural mesothelioma, in combination with cis-platinum and also for monotherapy treatment of NSCLC, locally advanced or metastatic. Pemetrexed® inhibits three enzymes (thymidylate synthase, dihydrofolate reductase, and glycinamide ribonucleotide transferase) involved in folate metabolism and DNA synthesis. Cytotoxicity of Pemetrexed® is caused by the inhibition of both pyrimidine and purine pathways (Thomas et al. 2009). Because of the high-symptom burden and severe morbidity, evaluation of the quality of life becomes important in these patients. The rationale of our investigation derives from reported data, showing that the integration with folic acid and B vitamins is a basic requirement to reduce the toxicity of Pemetrexed® therapy, resulting in better patient survival (Yang et al. 2013). Several observations have suggested that integration with "food-supplements" can reduce toxicity and improve the response during chemotherapy (Scagliotti and Novello 2003). During the last few years, pieces of evidence were accumulated regarding the increased antitumoral effect of administering the conventional chemotherapy, in combination with several antioxidants (de Giffoni de Carvalho et al. 2019). Moreover, natural products may be useful to improve the activity of anticancer agents. For example, the green tea polyphenol epigallocatechin-3-gallate (EGCG) has been shown in different studies to prevent cancer including lung cancer (Caltagirone et al. 2000). Specifically, in regards to lung cancer, EGCG has been demonstrated to induce cytotoxicity by the reduction of telomerase activity (Sadava et al. 2007). The major causes of chemotherapy-induced weight loss are adverse events such as nausea and vomiting. Nausea and vomiting cause reduced oral intake and have negative impacts on the quality of life (Miyahara et al. 2017). To prevent chemotherapy-induced weight loss, several nutrition interventions, such as dietary counseling and high-energy oral nutritional supplement, for patients with advanced cancer have been undertaken. However, these interventions did not show any improvement in nutritional parameters, due to the poor therapeutic results of nausea and vomiting, induced by chemotherapy. In short, these uncontrollable side effects have reduced the positive effects of nutritional interventions.

Texidrofolico® oral solution (Citozeatec Italy—FDA registration 12932524008 Pin n. bfJ3h263) is a nutritional supplement, whose formulation includes several compounds with high biological activity, including vitamin C, vitamin B5, vitamin B9, and vitamin D. Besides, Texidrofolico® contains components, which exhibits anti-inflammatory and immune-modulatory effects. A recent in vitro study has investigated the potential antiproliferative effect of Texidrofolico® on a human hepatocellular carcinoma cell line (Antonelli et al. 2019) and in patients with Prostate Carcinoma (Torricelli et al 2018). In these in vitro and in vivo models, Texidrofolico® was proven to be an excellent therapy adjuvant. These preclinical data have suggested the potential use of Texidrofolico® as an adjuvant in the treatment of patients with NSCLC. Following these findings, Texidrofolico® was investigated in a nutritional trial, as part of the chemotherapy of NSCLC, demonstrating, to date, an improvement in the quality of life of such patients.

Among the several biochemical alterations in cancer cells, one of the most consistent is the change in the intracellular polyamine content. Polyamines, putrescine (PUT), spermidine (SPD), and spermine (SPM) are small organic cations that are essential for normal cell growth and development in eukaryotes (Pegg 2016). Elevated levels of polyamines have been associated with breast, colon, lung, prostate, and skin cancers (Damiani and Wallace 2018), and found linked to differential regulation in cancer of the SAMe/nicotinamide methyl-donor pathway (Fahrmann et al 2017). Polyamines are considered potential biomarkers in a variety of cancers including lung cancer (Liu et al. 2017). Furthermore, metabolism and the requirement for polyamines in tumors are frequently dysregulated. Under normal physiological conditions, intracellular polyamine concentrations are tightly regulated through a dynamic network of biosynthetic and catabolic enzymes. From a clinical point of view, polyamine levels seem to have little diagnostic significance, but they can represent a reliable biomarker of neoplastic growth. In this regard, it has been reported that tissue SPD levels represent a significant prognostic factor for the recurrence of disease in cancer patients (Linsalata and Russo 2008). The reduction of plasma polyamine levels has a potential direct analgesic effect (Kergzien et al. 1996), mediated by the N-methyl-D-aspartate (NMDA) glutamate receptor and its NR2B unit, an ionic channel involved in pain perception (Loftis and Janowsky 2003). The potential reduction in plasma levels of plasma polyamines obtained with the administration of the food supplement, used in this study, could be an useful treatment for the management of patients undergoing chemotherapy that would improve their quality of life.

In conclusion, interventions with bioactive nutritional supplements, in combination with classic cancer drug treatments, could represent a promising strategy to increase the number of patients who could successfully respond to immunometabolic discomforts derived from chemotherapy.

Materials and methods

Reagents

All solutions were prepared with ultra-pure water (Millipore, Billerica, MA, USA). Chromatographic-grade solvents and reagents [acetonitrile, tetrahydrofuran, methanol, chloridric acid, and perchloric acid (PCA)] came from Mallinckrodt

Baker (Phillipsburg, NJ, USA). Tris(hydroxymethyl) aminomethane, boric acid, *ortho*-phtalaldehyde (OPA), β-mercaptoethanol, PUT, cadaverine (CAD), SPD, SPM, diaminooctane (DAO), trichloroacetic acid (TCA), and all reagents were from Sigma-Aldrich (St. Louis, MO, USA). Texidrofolico® oral solution was from Citozeatec (Italy).

Patients

To assess the effects of the dietary supplement (Texidrofolico®), a total of 30 patients under Pemetrexed® therapy were retrospectively enrolled as controls and some parameters were collected (Table 1). A stadiometer was used for height measurements and weight was recorded with a medical light beam scale at the baseline and at each point of time. The variation of body weight and the body mass index (BMI), observed after 90 days in untreated patients were compared with those observed in 30 Pemetrexed® plus Texidrofolico®-treated subjects. Initially, a preliminary assessment was made through a clinical psychological interview, a first nutritional visit, examinations to highlight any allergies to the product administered, and a battery of psychometric tests. The aim is to reconstruct the causes of the symptom, define the current situation, and identify the specific objectives for the subject. All patients who receive a mixture of Pemetrexed®–Texidrofolico® gave consent to receive Texidrofolico®, (60 mL administered orally twice during the day) as a diet supplement. The treatment with Texidrofolico® was carried out personally by the patient in the home environment according to a specific protocol (Torricelli et al. 2018). This type of program is preferred in cases where the psychological and also the clinical conditions of the patient are less compromised and the family picture presents itself as a resource to support the subject during the therapy. It should be noted that despite having requested the written consent of the patients and having respected the rules of the Helsinki Treaty, the opinion of an ethics committee was not necessary. Indeed the observational study presented is not a clinical trial, i.e., no drug has been tested. It was suggested to some individuals with lung cancer, to use a commercial food supplement sold in any spice and food supplement store, during their normal day at home. Furthermore, it was not a trial carried out in a hospital setting. The volunteers did not take toxic substances, did not interrupt the chemotherapy administered in the outpatient setting, and voluntarily reported the possible improvement of the adverse symptoms related to chemotherapy. In conclusion, it was an observational study in a non-hospital setting. Written informed consent was obtained from all individual participants included in the study. The effects of nutritional intervention in cancer patients were then carried out in an outpatient environment.

Nutritional therapy group

A professional dietitian individually counseled patients in the nutritional therapy group at three-time points (baseline, 6 weeks, and 2 months). To ensure reproducibility and consistency of individualized nutritional intervention, all patients in the nutritional therapy group were advised by the same dietitian, following a predetermined standardized procedure. In the first step, the dietitian assessed the history of usual and actual food intake, change in body weight, and problems with food intake using a defined form. Relevant aspects of the medical history (diagnosis; medical therapy; blood parameters; drugs; and symptoms such as weakness, cough, dyspnoea, nausea, pain, and hemoptysis), actual protein and energy intake, the quantity of fluid intake, and change of body weight over time were taken into account (Table 1). Patients had to complete a questionnaire about relevant factors influencing eating patterns (appetite, chewing ability, capacity to swallow, dysgeusia, allergies, psychological factors, and symptoms). Intake needed to fulfill energy requirements were calculated according to the Ireton–Jones formula (Ireton-Jones and Jones 2002). Protein requirements were set at 1 g/kg body weight daily. The weight of the treated patients was recorded before ($t=0$) and at the end ($t=90$ days) of the treatment and compared with the control group. BMI was calculated as weight in kg divided by height in meters squared.

Table 1 Patient characteristics of the study cohort

Parameters	Control ($n=30$)		Treated ($n=30$)	
Time (days)	0	90	0	90
Age (years)	61.13 ± 10.15	–	62.27 ± 10.33	–
Body height (cm)	174.33 ± 8.20	–	176.13 ± 5.98	–
Body weight (kg)	54.30 ± 12.88	48.00 ± 11.66*	55.20 ± 12.49	63.00 ± 10.14*
BMI	17.85 ± 15.79	15.79 ± 2.84*	17.73 ± 4.35	20.31 ± 3.81*

Mean ± SD

*$p<0.05$, compared with control patients

Preparation of samples and determination of plasma polyamines by high-pressure liquid chromatography

Blood sampling by finger puncture was performed according to "WHO Guidelines on Drawing Blood, 2010". Whole blood was immediately centrifuged at 500×*g* for 20 min after collection. The plasma was then removed for protein and polyamine assay, and the buffy coat leukocytes and erythrocytes discarded (Cooper et al. 1978). Aliquots of plasma (50–100 µL) were used for polyamine analysis. Protein-free plasma was obtained after treatment with 0.5 mL 7% PCA at 4 °C for 30 min. DAO was added as an internal standard (20 µM final concentration) and samples were centrifuged (14,000×*g* for 15 min). Pellet solubilized in 0.1 N NaOH was used for the determination of the proteins (Bradford 1976), whereas the supernatant was treated with 10 N KOH (2 N final concentration) for PCA neutralization. Potassium perchlorate was removed by centrifugation (15,000 × *g* for 20 min). The supernatant was filtered and the pH adjusted to 9.0 with 1 N HCl. OPA solution (4 mg/mL of methanol) was diluted with 1 M sodium borate buffer (pH 9.0) and β-mercaptoethanol (for a final volume of 5 mL: 4.74 mL sodium borate buffer, 0.25 mL OPA solution, and 10 µL β-mercaptoethanol). The OPA reagent may be stored at − 20 °C for 5 days. Samples were mixed with OPA reagent in a ratio 1:1. OPA-derivatized sample (100 µL) was injected into the HPLC column. The determination of OPA-derivatized polyamines was performed by AKTABASIC 10 HPLC apparatus (Pfizer, New York, NY, USA), equipped with a 100 µL sample loop. Reverse-phase separations were conducted at room temperature in an LC-18 Supelcosyl column (150 mm × 4,6 mm, 3 µm), equipped with a guard column Discovery HS C18 (2 cm × 4 mm, 3 µm) (Supelco, Bellefonte, PA, USA). The overall time of mixing of OPA with sample and injection was exactly 30 s (Provenzano et al. 2019).

Statistical

The results were expressed as mean and standard deviation. Comparison between groups was performed using Student's t test or the Mann–Whitney U test. For categorical data, Chi-square or Fisher's exact test was applied. Polyamine concentrations were obtained from calibration curves and expressed as mean ± SD. The results were presented as mean ± SD and analyzed statistically with Student's *t* test and the nonparametric Mann–Whitney test using SPSS 19.0 software for Windows (SPSS Inc., Chicago, IL). The threshold of significance was set at $P < 0.05$.

Results

Patients were evaluated for the potential variation of typical symptoms (anorexia, weakness, cough, dyspnoea, hemoptysis, and pain). Some basic clinical and laboratory evaluations were performed during the treatment (data not shown). Patients were recruited for the trial if they had undergone at least one course of chemotherapy and had at least one follow-up examination. Before each cycle, symptoms and quality-of-life data were collected with the Lung Cancer Scale (LCSS), as reported by Hollen et al. (1994). LCSS allows the evaluation of symptoms associated with chemotherapy of lung cancer and its effect on the state of the patient's quality of life. Symptoms significant changes were defined as changes from baseline, which were maintained for at least two cycles (60 days). In this case, the patients were considered symptomatic responsive. Symptoms have been classified as "improved, sporadic/stable or worsened", based on the pattern of change. Symptoms for patients without a confirmatory evaluation were classified as unknown. There was no adverse effect due to the intake of Texidrofolico® in any patient (data not shown). On the contrary, most of the patients taking Texidrofolico® reported a feeling of well-being. Improvement of appetite was recorded in 15 Texidrofolico®-treated patients (50%) and 10 patients (33%) of the group, which reported that they were feeling well after intake this food supplement. Symptomatology data, collected on NSCLC patients undergoing chemotherapy alone (Fig. 1a), or with Texidrofolico® (Fig. 1b) clearly show the improvement achieved following the administration of the dietary supplement. In particular, as shown in Fig. 1, some classic symptoms of chemotherapy have been drastically reduced. The interesting data obtained with the combined Pemetrexed®–Texidrofolico® therapy for 90 days concern the improvement of hemoptysis in 60% of the patients observed (Fig. 1a white columns), increasing the general "improved" data to 90% (Fig. 1b black columns). Another positive finding was the improvement of the symptoms of anorexia (− 28%), weakness (− 20%), cough (− 24%), dyspnoea (− 20%), and pain (− 16%), in patients treated with combined therapy (Fig. 1b white columns), with an evident increasing of the sporadic/stable symptoms (Fig. 1b grey columns).

Plasma polyamine levels in Pemetrexed®–Texidrofolico®-treated patients and in control subjects.

As presented in Table 2, plasma levels of PUT, SPD, and SPM were found to be higher in plasma of control subjects

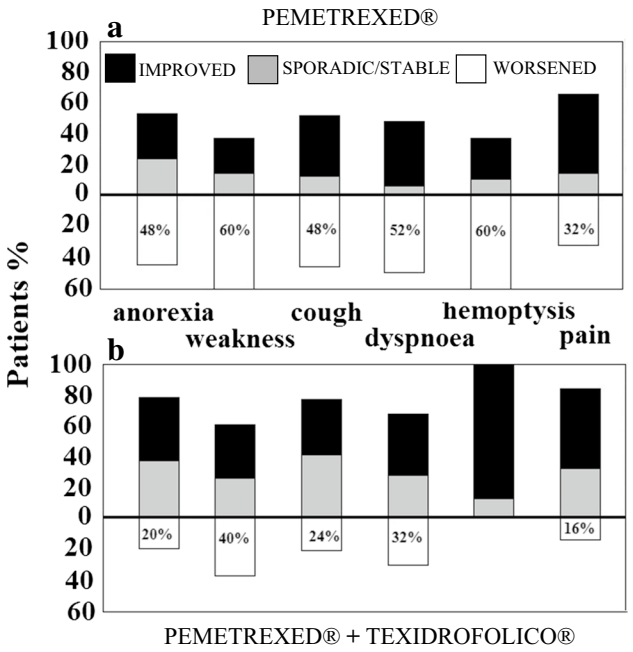


Fig. 1 **a** Data on the quality of life of patients with NSCLC at different stages, treated exclusively with Pemetrexed® therapy for 90 days. Evidence of the elements that make the quality of life worse (white columns), especially hemoptysis (60% of patients), weakness (60% of patients), and dyspnoea (52% of patients). **b** Data on the quality of life of patients with NSCLC at different stages treated with the Pemetrexed®–Texidrofolico® combined therapy for 90 days. There are improvements in the quality of life (sporadic/stable-grey columns), in particular markedly reduced hemoptysis (90% of patients-black columns), weakness, pain, and dyspnoea reduced by 20%. Improvements are evident compared to chemotherapy alone (reduction of white columns)

than in patients treated with Pemetrexed®–Texidrofolico®. PUT levels, particularly in control patients, appear increased by 42% during the 90-day observation period. In contrast, plasma levels of SPD (+ 14%) and SPM (+ 10%) appeared to be less increased. Texidrofolico®-treated patients showed plasma levels of the three polyamines, markedly reduced. From the data shown in Table 2, it can be seen that the plasma levels of the three polyamines appear markedly reduced following the combined treatment (Put-56%, SPD-56%, SPM-60%). By correlating these observations with the reduction of adverse events resulting from chemotherapy (Fig. 1), it would be possible to assume that these data could be useful to assess the quality of life of NSCLC patients. This potential biomarker could provide an innovative and effective way, not for the clinical diagnosis of lung cancer, but to stimulate a theoretical basis for the search for new tools to improve the quality of life of cancer patients.

Discussion

To improve the quality of life of the cancer patient, the difficulty of a participatory and communicative listening of doctors and nurses, perceived by patients, could be overcome with the help of psycho-oncology professionals. A correct and effective two-way communication between doctor and patient would lead, on one hand, to a better understanding of the patient's needs, including therapeutic needs, and, on the other hand, would reduce the patient's sense of anxiety and sometimes panic caused by fear of what is unknown. Beside this, another approach is needed to reduce the side effects of chemotherapy, which causes the patient's depression and fatigue and makes the therapy less acceptable. This paradigm is the object of the present study. In light of the serious quality-of-life problems in patients receiving NSCLC chemotherapy with Pemetrexed®, attempts were made to identify the potential predictors of these adverse side effects associated with this chemotherapy and how these factors led to the formulation of a nutritional intervention, seeking to improve its tolerability.

The most frequently reported side effects related to Pemetrexed® when used for NSCLC therapy are suppression of bone marrow function that occurs with anemia, neutropenia, leukopenia, thrombocytopenia, and gastrointestinal toxicities that manifest with anorexia, nausea, vomiting, diarrhea, constipation, pharyngitis, mucositis, and stomatitis (Lin et al. 2017). Pemetrexed® is a multi-target antifolate, because it inhibits thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide-ribonucleotide-formyl transferase (GARFT), key folate-dependent enzymes for the novo biosynthesis of the nucleotides thymidine and purine.

Table 2 Plasma polyamine levels of NSCLC patients

pmol/mL	Putrescine		Spermidine		Spermine	
	$t=0$	$t=90$	$t=0$	$t=90$	$t=0$	$t=90$
Control subjects $n=30$	0.095 ± 0.015	0.135 ± 0.025	0.180 ± 0.028	0.205 ± 0.035	0.200 ± 0.032	0.220 ± 0.042
Pemetrexed® Texidrofolico® patients $n=30$	0.102 ± 0.009	0.045 ± 0.012*	0.243 ± 0.045	0.108 ± 0.012*	0.188 ± 0.055	0.075 ± 0.021*

Mean ± SD

*$p < 0.05$, compared with control patients

Pemetrexed® is removed unmodified by tubular secretion at the renal level and partly by glomerular filtration. Folates are essential vitamins for cell proliferation, because they are indispensable in the process of DNA building. It has been observed that high production of polyamines increases the demand for folates in the cell, which is necessary for normal cellular metabolism.

The tumor secretes high levels of polyamines, which are released into the extracellular environment and stimulate cell proliferation. Polyamines are small organic cations essential for normal cell growth and eukaryotic development (Pegg 2016). In physiological conditions, the concentration of intracellular polyamines is regulated by a series of biosynthetic and catabolic enzymes. This strict metabolic regulation is altered in tumor growth; in fact, in many tumors, the plasma concentration of polyamines is markedly increased (Damiani and Wallace 2018). It has been observed that treatment with Texidrofolico®, in patients undergoing chemotherapy, has significantly reduced the level of plasma polyamines. Although it is not yet possible to highlight a precise relationship between these data and the improvement of the general conditions of the treated patients, we could preliminarily assume that the polyamine pathway may be a rational objective to be investigated. Concerning the identification of potential predictors of severe toxicity associated with Pemetrexed® and the consequent poor quality of life, the results presented appear to highlight that the level of polyamines in plasma may represent a potential indicator of the patient discomfort. Further studies will be necessary to confirm this preliminary observation. As mentioned, the synthesis of polyamines is closely linked to the metabolism of folates (Bistulfi et al. 2009). Indeed, folates are needed for the synthesis of S-adenosylmethionine (SAMe), which is involved in the synthesis of polyamines. Folate deficiency reduces the SAMe cell pool, which should, therefore, result in a decrease in polyamine synthesis. Conversely, one study reported that a folate-depleted diet does not decrease polyamine levels, but surprisingly increases them in the blood and liver of rats, likely as a consequence of a compensatory response (Sun et al. 2002).

Under normal conditions, the body neutralizes biogenic amines through special enzymes such as monoamine oxidase (MAO) and diamine oxidase (DAO) and, of course, the detoxifying action of the liver. The increase in plasma levels of polyamines, found in tumors, could render the detoxification mechanism insufficiently active, causing the typical symptoms of the toxicity of aliphatic amines (Greim et al. 1998).

For this reason, the possibility that an increased plasma level of biogenic amines may cause adverse side effects associated with chemotherapy depends on the effectiveness of the detoxification systems, which, under normal conditions, are such as not to cause symptoms. Based on this consideration, it could be argued that the decrease in adverse chemotherapy symptoms, reported in this investigation, could result from the reduction of plasma levels of polyamines in patients treated with the dietary supplement under investigation. In support of this hypothesis, it is useful to consider that among the components of Texidrofolico®, the B vitamins and folic acid are present in considerable quantities. Furthermore, several scientific publications reported that the clinical treatment of NSCLC patients with Pemetrexed® supplemented with folic acid and B vitamins significantly reduces the toxicities associated with chemotherapy (Scagliotti and Novello 2003).

It is noteworthy that the reduction of plasma polyamines has a potential direct analgesic effect; indeed, their deprivation has been reported to cause analgesic effects in animals subjected to various painful stimuli (Kergzien et al. 1996). This analgesic effect is mediated by NMDA–glutamate receptor and its NR2B unit, and an ion channel widely distributed in the nervous system is implicated in pain perception (Loftis and Janowsky 2003). Since exogenous administration of SPM in mice produced NMDA receptor activation and various discomforts, it was assumed that this polyamine was directly involved in nociception (Gewehr et al. 2011). The pieces of evidence presented in this report suggest that the administration of a food supplement such as Texidrofolico® may reduce the side effects of lung cancer's chemotherapy, probably as a result of reduced blood levels of biogenic polyamines.

In conclusion, the impact on a patient's quality of life must be a fundamental parameter for establishing the value of a new anticancer drug. Determining clinical effectiveness alone is no longer sufficient. This process is inevitable in the light of the proposal for an European Regulation on Health Technology Assessment (HTA), presented in January 2018 in Brussels.

Compliance with ethical standards

Conflict of interest There is no conflict of interest.

Ethical standards The reported observational study is not intended as a clinical trial. All procedures performed involved human participants were in accordance with the ethical standards and with the 1964 Helsinki Declaration and its later amendments.

Informed consent The authors state that all patients gave their informed consent prior to their inclusion in the study.

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