

RESEARCH ARTICLE

PREVENTION OF OXALIPLATIN-INDUCED PERIPHERAL NEUROPATHY IN COLORECTAL CANCER: THE PLANET TRIAL EXPERIENCE

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ABSTRACT

Oxaliplatin-induced peripheral neuropathy (OIPN) is a common side effect in patients receiving chemotherapy for colorectal cancer (CRC) and it remains the most frequent dose-limiting toxicity, affecting especially quality of life (QoL) of patients. The best known pathogenetic mechanisms is the production of reactive oxygen species (ROS) and their negative activity at the axonal level. Consequently, medical research focused on the hypothesis that antioxidant substances may be efficacious in preventing OIPN. The purpose of our work is to report the experience of the PLANET trial (Oxaliplatin Neurotoxicity Prevention Trial) and provide a constructive discussion on one of the oncological toxicities still today little controlled by medical therapies.

The PLANET trial was a monocentric, prospective, randomized, placebo-controlled, double blind, phase II clinical study designed to investigate if the

association of vitamin E and super oxide dismutase (SOD) is able to prevent OIPN in colorectal cancer patients receiving oxaliplatin-based chemotherapy regimens. Primary endpoint was the assessment of OIPN incidence and severity in the two treatment arms. Secondary endpoints were the correlation between the OIPN and the oxaliplatin dose in terms of symptoms intensity, type of neuropathy and quality of life; finally the OIPN duration along the follow-up checks. 47 patients with CRC, operated or in advance stage, candidates for oxaliplatin-based chemotherapy, were enrolled from January 2014 to October 2015 in our Center and randomized into the two groups, the experimental arm (24 patients) and the placebo arm (23 patients). The study included an analysis of at least 18 months, 6 of treatment and 12 of follow-up. In the global cohort analyzed, 32.5% of patients reported development of pares-

thesias during chemotherapy treatment, with an increase of symptoms intensity in cycles progression of active treatment and a reduction during follow-up. After 12 months of follow-up, 50% of participants experienced complete relief of paresthesias while 50% had persistent symptoms. But the most important finding was the lack of statistical differences between the two arms in terms of neuropathy incidence, toxicity and variations in QoL.

OIPN represents a still poorly understood oncological toxicity. In addition to oxidative stress, there are other pathogenetic mechanisms, partly clear and partly unknown. Scientific research is trying to better study them and to develop efficacious treatment strategies against this toxicity. Over the years there have been many attempts to use various

drugs but with unsatisfactory results. Our PLANET experience leads us to conclude that the association of vitamin E and SOD has not proved efficacious in preventing the OIPN. The main reasons are due to the smallness of the sample analyzed and the pathogenetic complexity of the phenomenon in which oxidative stress represents, according to medical literature, only a part of the mechanisms responsible for the OIPN. The positive note is that the treatment has a good tolerance. OIPN remains an open chapter of oncology for which more information is needed in order to identify an efficacious treatment strategy. The prevention of this toxicity would allow a better management of platinum-based chemotherapy and an improvement in the quality of life of patients.

KEY WORDS

Oxaliplatin-induced peripheral neuropathy; colorectal cancer; vitamin E; super oxide dismutase.

IMPACT STATEMENT

With our work, mainly addressed to oncologist colleagues dealing with gastrointestinal malignancies, we wish to provide our monocentric experience on one of the still unresolved chemotherapy toxicities.

INTRODUCTION

Colorectal cancer (CRC) represents the third most frequent oncological disease in men and women. Despite this high incidence, the mortality is low with a greater than 60% 5-years overall survival.

Over the few last decades there is an increase in survival, related to early diagnosis and treatment improvements (1). One of the most widely used treatment regimens, in both early and advanced patients, is oxaliplatin-based chemotherapy. Oxaliplatin is a third-generation platinum compound with a significant antineoplastic activity. It forms an essential part of colorectal cancer neoadjuvant, adjuvant and even in palliative chemotherapy regimens, particularly in combination with 5-FU and leucovorin in FOLFOX or in XELOX regimens. Its mechanism of action involves the cross-linking with the strands of DNA, inhibiting DNA replication and transcription (2-4). Like all drugs, especially oncological ones, oxaliplatin also has side effects. The main one is the peripheral neuropathy (5). Oxaliplatin-Induced Peripheral Neuropathy (OIPN) occurs in two distinct forms. Firstly, it appears as an acute cold-triggered sensory neuropathy which affects 85-90% of pa-

tients and which develops shortly after infusion of the drug with symptoms like paresthesias and/or disesthesias in the distal extremities, in the perioral region and rarely in the throat. Symptoms reach their peak three days after administration, then tend to subside over the next 7 days. The second form of OIPN is a chronic neuropathy which affect 10-15% of patients and which is correlated with the cumulative dose of oxaliplatin administered; it involves sensory loss, sensory ataxia and changes in proprioception. Common symptoms include numbness, tingling and/or burning pain. This type of neurotoxicity persists throughout treatment and increases in intensity with cumulative dose; symptoms resolve within 6-12 months of cessation of therapy, but in a small group of patients, symptoms persist for more than one year (6-8).

This oncological toxicity, both in the acute and in the chronic form, interferes with the patient's daily activities, negatively affecting his quality of life (9, 10). Regarding the pathogenetic mechanisms of OIPN, the best known is certainly the oxidative stress and the consequent axonal damage (11). Medical

research has therefore focused on the hypothesis that antioxidant substances may be efficacious in preventing this problem (12).

The purpose of our work is to report the experience of the PLANET trial (Oxaliplatin Neurotoxicity Prevention Trial) and provide a constructive discussion on one of the oncological toxicities still today little controlled by medical therapies.

MATERIALS AND METHODS

Study design, endpoints and evaluation systems

The PLANET trial was a monocentric, prospective, randomized, placebo-controlled, double-blind, phase II clinical study which evaluated the efficacy of a combination of vitamin E in the form of tocotrienols (Tocomax™) and super oxide dismutase (SOD) in preventing peripheral neuropathy in colorectal cancer patients. The study therefore had two arms: the experimental one consisting of the pharmacological combination and the control one based on placebo. The primary endpoint was the assessment of OIPN incidence and severity between the two treatment arms. The secondary endpoints were the correlation between the OIPN and the oxaliplatin dose in terms of symptoms intensity, type of neuropathy and quality of life; finally, the OIPN duration along the follow-up checks.

The primary endpoint was assessed through the functional medical evaluation which attested the appearance of OIPN and its preliminary gradation according to the NCI-CTCAE (National Cancer Institute - Common Toxicity Criteria for Adverse Events). Oncologist assigned a score as follows: 0 = normal; 1 = weakness on physical exam and/or loss of reflexes or paresthesias not interfering with daily function; 2 = weakness and sensory alterations interfering with daily function; 3 = weakness and sensory alterations interfering with activities of daily living or requiring bracing or assistive devices; 4 = life threatening, paralysis, disabling (13). For the assessment of the secondary endpoints, the patient questionnaires were added to the functional medical evaluation. These were completed at baseline, prior to the start of treatment, at 3 and 6 months and every three months after treatment cessation during the 12 months of follow-up.

We selected two questionnaires validated and promoted by the EORTC (European Organization for

Research and Treatment of Cancer). The first was the QLQ-CIPN20 (Quality of Life Questionnaire - Chemotherapy Induced Peripheral Neuropathy) which evaluated the link between the cumulative exposure to oxaliplatin and each aspect of the OIPN such as the type of neuropathy, the intensity of symptoms and the implications on quality of life. This tool included 20 items measurable through a Likert scale ranging from 1 (not at all) to 4 (very much); scores were linearly transformed to 0-100 scale (14).

The second questionnaire was the QLQ-C30 (Quality of Life Questionnaire - Cancer) which assessed the quality of life of patients in relation to a large spectrum of physical, psychological and cognitive symptoms, not necessarily due to OIPN; each item was scored from 1 (not at all) to 4 (very much), except for the global QoL perception which ranged from 1 (very poor) to 7 (excellent). Similarly, to the first, also in this questionnaire the scores obtained were transformed into a 0-100 scale (15).

Finally, the same tools were used to define the OIPN duration after 3, 6, 9, 12, 15 and 18 months from the start of treatment.

Pharmacological rationale

In our experience we decided to use the combination of vitamin E and superoxide dismutase. These are two antioxidant substances that play a central role in fighting free radicals. Vitamin E is a powerful antioxidant which neutralizes reactive oxygen species (ROS) and actively protects cells from oxidative stress and in particular from lipid peroxidation. Superoxide dismutase, on the other hand, is an endogenous enzyme present in most human tissues which converts ROS into hydrogen peroxide, thus contributing to the reduction of oxidative stress.

We chose to use this drug combination for two main reasons: first of all, the best known and studied pathological mechanism of oxaliplatin-induced neuropathy is just the peripheral axonal damage due to oxidative stress. Secondly, we exploited the positive results of some preliminary studies which demonstrated the efficacy in the use of these molecules to prevent oxaliplatin neuropathy (12).

Patients population, analysis time and treatment plan

Colorectal cancer patients aged 18 years or more, with a good performance status (ECOG 0,1) were assigned to adjuvant or palliative chemotherapy with oxaliplatin after obtaining informed consent.

Preexisting or actual neuropathy from any other cause - mellitus diabetes, chronic alcoholism, malnutrition or vitamin B deficiency, prior exposure to chemotherapy, pregnancy, and gluten intolerance were exclusion criteria. Forty-seven patients were enrolled from January 2014 to October 2015 in our Center, from a total of 80 expected patients. Due to a slowdown in enrollment, the study was closed early. The diagram in **figure 1** illustrates patients' flow-chart. Baseline characteristics were equivalent for the two treatment arms and are reported in **table I**. Thirty-eight patients were operated and received adjuvant chemotherapy while nine patients were in advanced stage and received palliative chemotherapy. Of the total 47 patients, 24 were assigned to the experimental arm and 23 to the control arm. The study included 18 months of analysis with a minimum of 6 months of active therapy and 12 months of follow-up. Treatment interruption before 6 months, because of toxicity or early chemotherapy discontinuation, was considered in the statistical analysis. The drug combination was registered as Reclex® but, for the purpose of our study, it was made clearly unrecognizable. Reclex® retard enteric-coated controlled-release pills were administered daily during the whole chemotherapy treatment period (6 months). Even if one or more cycles of oxaliplatin were not administered the antioxidant drug was maintained. Drug administration was interrupted only in cases of severe oxaliplatin side effects. Patients were dropped from the trial if treatment was interrupted for more than seven days.

STATISTICAL ANALYSIS

All patients were recruited, treated and followed-up at the Medical Oncology Unit of IRCCS San Matteo Hospital of Pavia, in Italy. Patients were randomly assigned to Reclex® or placebo groups. The sample size required (40 patients for each group) was calculated from the hypothesized difference of 40% (control group) versus 10% (Reclex® group) in the neurotoxicity rate when power is set at 80%. Calculations used two-sided t tests with alpha error set at 0.05. Expecting a 10% of drop out, a total of 80 patients were considered for recruitment. Efficacy assessment is primarily conducted on an "intention-to-treat" approach. All randomized patients have been included in the data analysis: in cases of drop out and interrupted follow-up, patients were considered as not having achieved

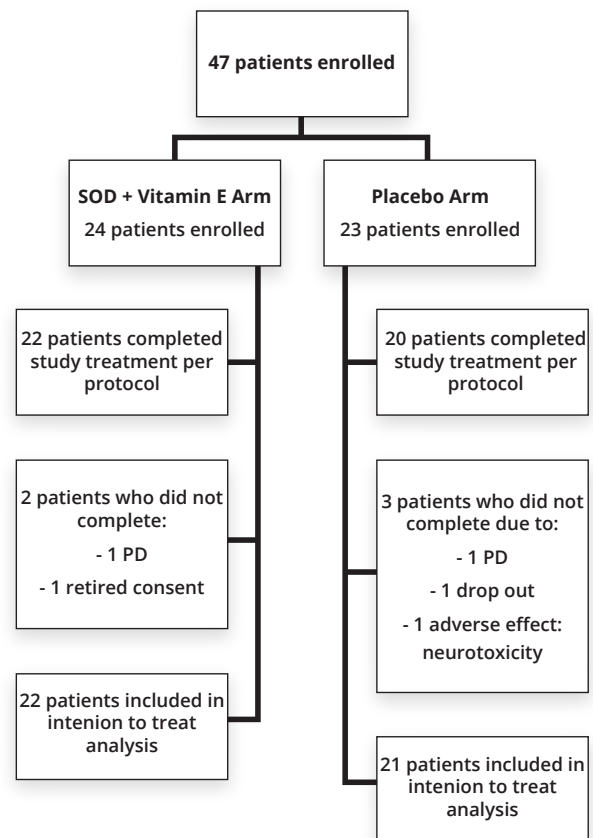


Figure 1. Patients flow-chart.

endpoint. Frequencies and percentages were calculated for qualitative data and comparisons were analyzed using chi-square test or Fisher exact test, as appropriate. Mean and standard deviation were used for describe quantitative variables, if normally distributed, otherwise median and interquartile range (IQR) were used. A t test for independent data (or equivalent non parametric test) was used to compare quantitative variables between two group. Linear regression models for repeated measures were used to analysis the changes over time of EORTC-CIPN20 and QLQ-C30 scores. Data were express as monthly change means with theirs Standard Errors (SE). A value of $p < 0.05$ was considered statistically significant. All tests were two-sided. The data analysis was performed using the STATA statistical package (version 15.0, 2017, Stata Corporation, College Station, Texas, USA).

RESULTS

Of the total 47 patients, 43 were analyzed as intention to treat population. Regarding the prima-

	RECLEX® RETARD (NO 24)	PLACEBO (NO 23)	ALL	P
Median Age (IQR)	59.0 (53.1 – 65.5)	64.6 (60.9 – 68.4)	62	0.0370
Female (%)	6 (25.0)	5 (21.7)	11	0.792
STAGE				
C1/C2 D	18 (47) 6 (67)	20 (53) 3 (33)	38 9	0.461
PLANNED CHEMOTHERAPY REGIMEN (%)				
XELOX FOLFOX4 FOLFOX6 (± bevacizumab or panitumumab)	4 (16.7) 14 (58.3) 6 (25.0)	9 (39.1) 11 (47.8) 3 (13.0)	13 25 9	0.211
COMPLETED TREATMENT				
XELOX FOLFOX4 FOLFOX6 (± bevacizumab or panitumumab)	3 (12.5) 14 (58.3) 5 (20.8)	9 (39.1) 9 (39.1) 2 (8.7)	12 23 7	0.075

Table I. Baseline patient characteristics.

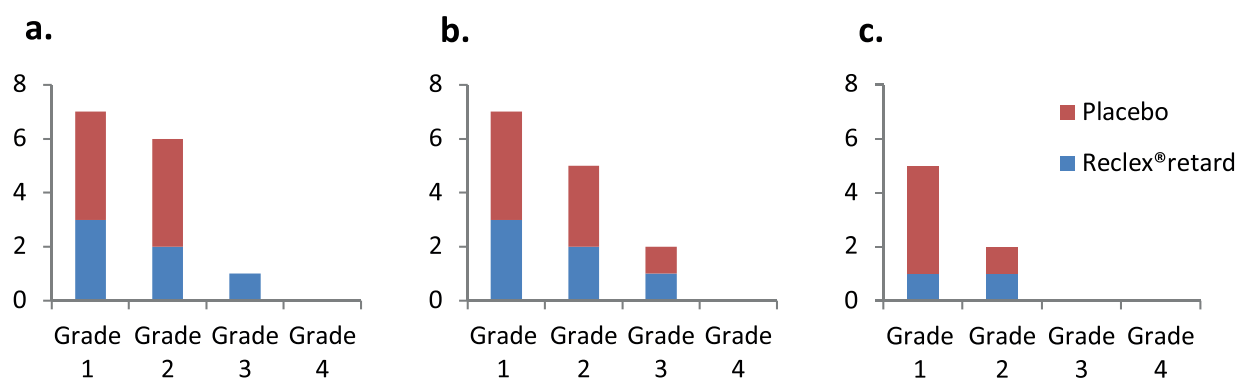


Figure 2. a. Distribution of NCI-CTCAE grading of paresthesia at appearance; b. at the end of chemotherapy; c. after 12 months follow-up.

ry endpoint of the study, the incidence rates and grades of neurotoxicity were assessed during treatment, at the end of treatment and after 12 months of follow-up. During chemotherapy, 14 patients (32,5% of total) reported development of paresthesias. Incidence of NCI-CTCAE grades is described in **figure 2**. We observed an increase of symptoms intensity during active treatment and a reduction during follow-up (**figure 3**).

For the secondary endpoints, the QLQ-CIPN20 questionnaire showed no significant difference between treatment arms in terms of OIPN incidence, evolution, type of neuropathy, symptoms intensity and quality of life (**figure 4**). The average monthly change of the QLQ-C30 scores is reported in **table II**. Similar-

ly, there were no differences between the two arms in terms of non-neurological toxicities evaluated using the second questionnaire (**figure 5**). Reported side effects can be attributed to known toxicity associated with chemotherapy and not to experimental compound or placebo. Therefore, SOD/tocotrienols association with chemotherapy was well tolerated. After 12 months of follow-up, 50% of participants experienced complete relief of paresthesias, while 50% had persistent symptoms, in most cases with grade 1, although 2 patients still had grade 2. Our results partially reflect literature data on the incidence of paresthesias. The trial showed neurotoxicity in 32,5% of patients, a percentage slightly lower compared to the values present in

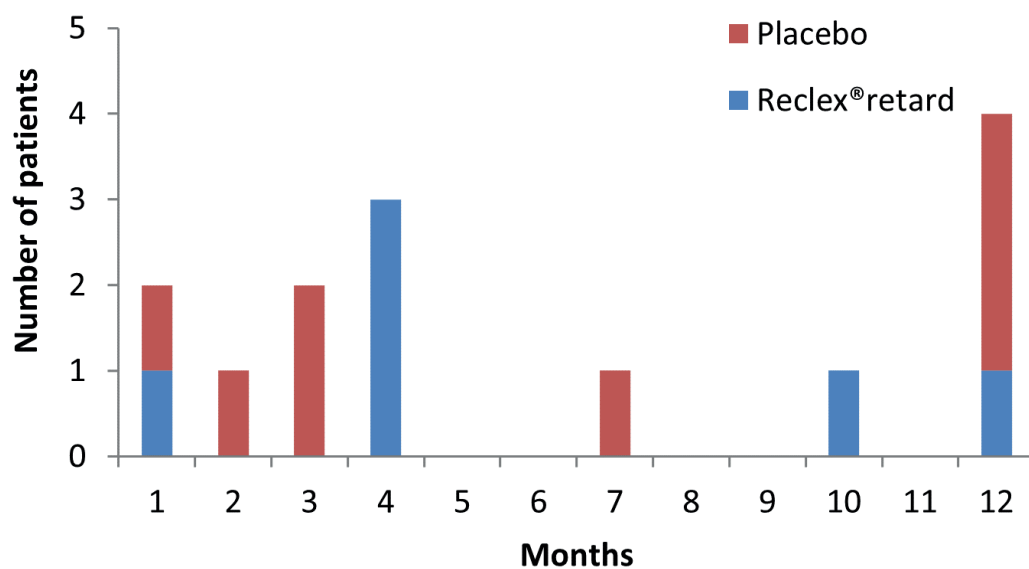


Figure 3. Duration of paresthesias; in majority of cases paresthesias resolved within 4 months. Some patients still have experience of symptoms after 7, 10 months or after termination of follow-up period (12 months).

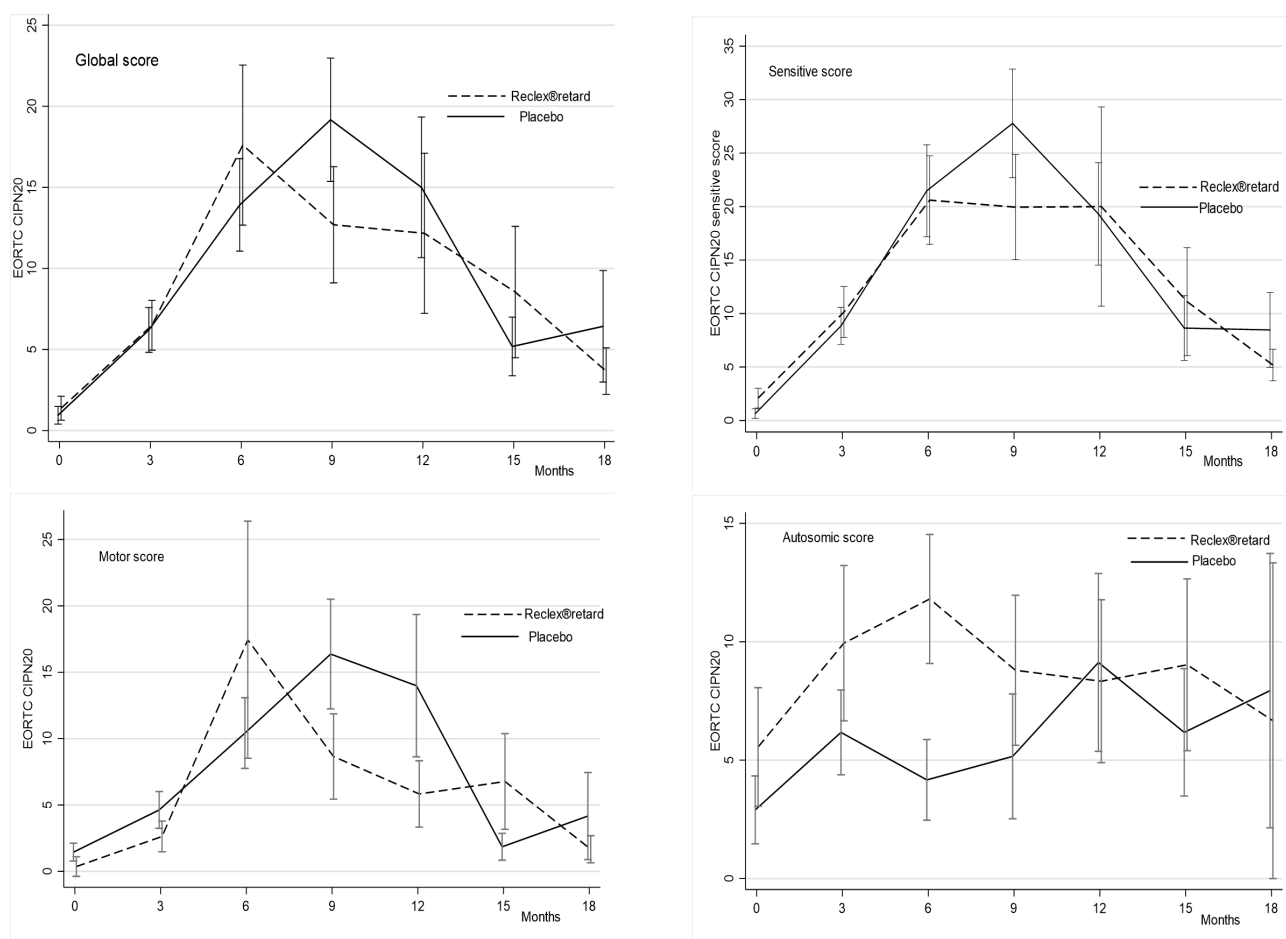


Figure 4. Results of QLQ-CIPN20.

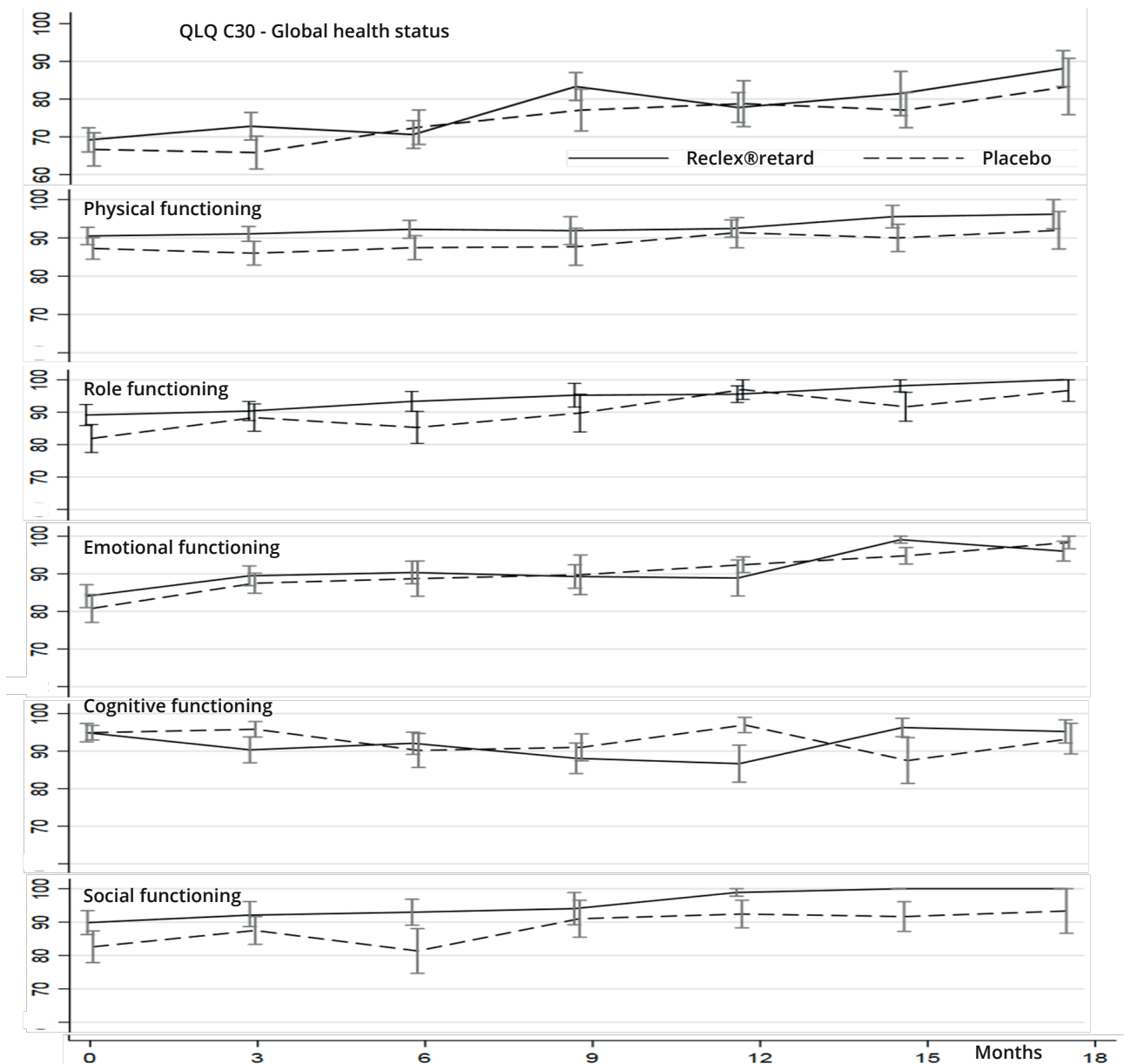


Figure 5. Results of QLQ-C30.

literature (40-50% as mean value). However, grade 3 incidence is similar (9,3% in PLANET trial vs 10-20% in literature). In the literature, symptoms are reported to be reversible within 6-12 months after treatment conclusion. Similarly, in the PLANET trial, relief occurred in 6-12 months with a median of 4 months (6-8).

DISCUSSION

The exact mechanisms underlying the OIPN are unclear. It has been proposed that the acute form is a result of increased excitability of peripheral neurons caused by functional impairment of cur-

rents through Na^+ voltage-gated ion channels in nerve membranes after the chelation of calcium by oxalate, a metabolite of oxaliplatin. Chronic neuropathy results instead from the accumulation of platinum in dorsal root ganglion cells. A well-known pathological mechanism at the base of OIPN is the production of free radicals; these affect the integrity of the axonal membranes altering the correct conduction of nerve impulses (5-8, 11).

In the literature there is much evidence that several classes of chemotherapy agents, including Oxaliplatin, can lead to the formation of ROS (16). This is the reason why medical research promoted the use of antioxidants in the prevention of OIPN. The most varied molecules with antioxidant activi-

	MEAN	SE	P
GLOBAL HEALTH STATUS	0.97	0.19	< 0.001
PHYSICAL FUNCTIONING	0.3	0.13	0.024
ROLE FUNCTIONING	0.71	0.14	< 0.001
EMOTIONAL FUNCTIONING	0.73	0.13	< 0.001
COGNITIVE FUNCTIONING	- 0.16	0.17	0.356
SOCIAL FUNCTIONING	0.66	0.17	< 0.001
FATIGUE	- 0.61	0.17	0.001
NAUSEA AND VOMITING	- 0.20	0.06	0.002
PAIN	- 0.38	0.15	0.012
DYSPNEA	0.02	0.16	0.879
INSOMNIA	- 0.53	0.19	0.008
APPETITE LOSS	- 0.34	0.14	0.022
CONSTIPATION	- 0.29	0.25	0.246
DIARRHEA	0.04	0.15	0.795
FINANCIAL DIFFICULTIES	- 0.26	0.25	0.303

Table II. Average monthly change of QLQ-C30.

ty were tested, the main ones being vitamin E and glutathione. Overall, no specific molecule has been shown to be efficacious in preventing neurotoxicity; the best and most encouraging results were obtained with the use of glutathione (12, 17-20).

The following are the most significant studies on the other substances most frequently used in the management of oxaliplatin-induced neuropathy.

Let's start from the Acetyl-L-carnitine; this is an enzyme which transports fatty acids into the mitochondria and appears to have an antioxidant action in the nervous system. Nevertheless, its efficacy in preventing OIPN has not been proven (21). Another substance put under the magnifying glass of scientific research is the Alpha-lipoic acid; it is an antioxidant molecule particularly active in the liver and nervous system. The only randomized study on its use concluded that it is unable to prevent OIPN and is also poorly tolerated (22).

A positive glimmer seemed to come from the intravenous administration of calcium and magnesium; several studies documented its efficacy without

however obtaining a subsequent confirmation in the randomized and controlled clinical trials (23-30).

The role of cannabinoids was studied in a small randomized trial which, however, was negative (31). Some researchers focused on cryotherapy and compression techniques, often combined, obtaining discordant results; in some trials it would seem that the techniques have a positive result in the management of OIPN in others they do not (32-40).

One substance which seemed promising is metformin which in a small randomized trial it shown to reduce the severity of oxaliplatin-induced neuropathy compared with the control arm. Clearly, more studies are needed to confirm its efficacy (41).

Many studies focused on the antiepileptic and antidepressant drugs. Gabapentin and pregabalin appear to produce positive effects on OIPN but without evidence confirmed by large-scale clinical studies (42-44). In the EFOX trial, Durand et al. demonstrated a clear efficacy of venlafaxine in preventing OIPN; in contrast, Zimmerman and colleagues failed to confirm any benefit using this drug (45, 46). The only drug in this class that has been shown to be efficacious in the management of chemotherapy-induced neuropathy is duloxetine. But its efficacy, as can be easily imagined, still needs to be validated (47-49).

Afterwards the research focus shifted to molecules with neuroprotective activity. Mangafodipir is a chelate of manganese which seemed to reduce OIPN-related symptoms but its systematic use is not recommended due to the neurological toxicity resulting from the compound (50). Other neuroprotective molecules like amfostine, N3-polyunsaturated fatty acids, xaliproden, analgescine have been studied with promising effects in a few small trials (51-54).

Given the lack of real efficacy of global results, traditional oriental medicine has even been applied and in particular the role of herbs with a detoxifying action or the acupuncture. Again, the final results are negative (55-58).

Despite positive results obtained in several trials, there are no recommendations for any of these substances. Further prospective, randomized, controlled trials with larger sample sizes are needed to confirm these findings and to verify the clinical value of these agents in the management of OIPN. But most of all, what is now evident is that the

pathogenesis of this problem is multifactorial, with partly still unknown mechanisms. Scientific research is trying to better study them and to develop efficacious treatment strategies against this toxicity.

The only useful approach that remains to oncologists is the management of oxaliplatin-based chemotherapy and more specifically the application of strategies such as dose reduction, slowing the infusion rate or the "stop and go" strategy. OP-TIMOX and CONcePT are two of the trials which have supported these OIPN prevention and treatment strategies (59-60).

The American Society of Clinical Oncology (ASCO) recently published the guidelines for the prevention and management of chemotherapy-induced peripheral neuropathy; it is a monumental review of the literature on the subject that rigorously analyzes nearly 40 substances, classifying them by strength of recommendation, evidence and clinical benefit. The innovative purpose of this work is the revision of randomized studies on the use of the analyzed substances in order to draw general and non-anecdotal conclusions. The ASCO expert panel confirms the appropriateness of clinical strategies for reducing or discontinuing chemotherapy and recognizes, with a moderate level of benefit, the treatment of OIPN with duloxetine reserving to obtain further data from subsequent and more targeted studies (61).

CONCLUSIONS

Our PLANET experience leads us to conclude that the association of vitamin E and SOD has not proved efficacious in preventing the OIPN. The main reasons are due to the smallness of the sample analyzed and the pathogenetic complexity of the phenomenon in which oxidative stress represents, according to medical literature, only a part of the mechanisms responsible for the OIPN. The positive note is that the treatment has a good tolerance.

As happens in most monocentric studies, a limit to be dealt with is just the small sample of patients studied which understandably affects the non-generalizability of the results obtained. Nevertheless, given the lack of solid data on this topic, we decided to publish our experience anyway, net of the final results. When we realized our work the ASCO guidelines had not yet been published so we based on preliminary studies which showed some

positive result on the pharmacological activity and on the clinical benefit of the substances used. The most important review we have today expresses a negative opinion on antioxidant substances, including vitamin E and superoxide dismutase, in the management of OIPN, which is consistent with our small experience (61).

A methodological limitation is represented by the use of questionnaires for patients to assess the intensity of neuropathy, which, however well compiled, remain absolutely subjective tools. The choice of this system, nevertheless, is due just to the fact that the symptoms of neuropathy, from paresthesia to pain, are subjective experiences for which there are no validated tools able to change the symptom in a clinical sign perfectly objective; to do this, it is necessary to use specialized tests, such as electroneuromyography, which on the whole are expensive, require specialized staff and do not represent ideal and flexible methods to be used frequently as in our study (62). Finally, we can say that the antidote for this toxicity may not be a single drug but maybe a combination of several active molecules which reflects the multifactorial nature of problem.

OIPN remains an open chapter of oncology for which more information is needed in order to identify an efficacious treatment strategy. The prevention of this toxicity would allow a better management of platinum-based chemotherapy and an improvement in the quality of life of patients.

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ETHICS

Fundings

There were no institutional or private fundings for this article.

Conflict of interests

The authors have declared no conflict of interests.

Availability of data and material

All the data supporting the findings of this study are available within the article and can be shared

just before a reasonable request to the corresponding author.

Authors' contribution

SA had the idea of the project and oversaw the drafting of it in each section; RT, FS, TM, CG, AF edited the sections Introduction, Materials and Methods, Results and Conclusions; CT dealt with

the statistical processing and the specific Statistical analysis section; SB supervised the entire work, working in detail in the Discussion section.

Ethical approval and consent to participate

The study was approved by the local ethics committee of the Politecnico San Matteo (Pavia, Italy) in compliance with the Declaration of Helsinki.

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