FINAL RESULTS OF THE BREAST CANCER COHORT OF THE STEFANO TRIAL

REDUCTION OF SEVERITY OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY BY ONLIFE

M. Zaiss[1]
J. Uhlig[2]
M.-O. Zahn[3]
T. Decker[4]
H. Lehmann[5]
J. Harde[6]
C. Hogrefe[7]
C. Vannier[8]
N. Marschner[1,8]

1 Praxis für interdisziplinäre Onkologie & Hämatologie GbR, Freiburg i. Br., Deutschland

2 Praxis Dr. med. Uhlig, Naunhof, Deutschland

3 Überörtliche Berufsausübungsgemeinschaft MVZ Onkologische Kooperation Harz, Goslar, Deutschland

4 Studienzentrum Onkologie Ravensburg, Deutschland

5 Universitätsklinikum Köln (AöR), Köln, Deutschland

6 Department of Data Management, Statistics and Medical Informatics, iOMEDICO, Freiburg i. Br., Deutschland

7 Clinical Operations, iOMEDICO, Freiburg i. Br., Deutschland

8 Medical Department, iOMEDICO, Freiburg i. Br., Deutschland

INTRODUCTION

Chemotherapy (CTx)-induced peripheral neuropathy (CIPN) is a common and potentially dose-limiting side effect of neurotoxic CTx, especially of platinum and taxanes, with a profound impact on patients' quality of life and survivorship. It is predominantly caused by sensory axon damage. There is no effective strategy to prevent or cure CIPN.[1]

OnLife® is a dietary supplement that contains a patented mixture of fatty acids (Fatty Acids Group (FAG®), comprising (poly)unsaturated Omega-3, -6, -9 fatty acids and saturated fatty acids) and the fatty acid amide palmitoylethanolamide (PEA).[2–5]

Fatty acids, in particular polyunsaturated fatty acids (PUFAs), are essential in normal physiology and metabolism of the central and peripheral nervous system through their role in several biochemical functions, including nerve cell and myelin membrane composition and fluidity, intracellular signaling, synthesis of anti-inflammatory mediators, and gene expression. Reduced fatty acid levels result in the development of peripheral neuropathy by the alteration of myelin structure and function.[6] Supplementation with fatty acids has been shown to have preventive and therapeutic effects in many psychiatric[7] and neurodegenerative diseases[8], including CIPN[9].

The fatty acid amide PEA, that belongs to the class of endogenous cannabinoids, has been shown to have anti-inflammatory, antinociceptive, analgesic, neuroprotective and anticonvulsant properties.[10] Treatment with exogenous PEA is effective and safe in various neuropathological conditions[11], including chronic idiopathic axonal neuropathy[12], diabetic neuropathy[13], nerve compression syndromes[14], as well as CTx-induced neuropathic pain[15].

CONCLUSION

Results of the STEFANO study show that about one third of patients with paclitaxel induced CIPN had a clinically relevant reduction in the severity of sensory neuropathy after treatment with OnLife®. According to patient-reported outcomes this effect was even clearer with 45% of patients reporting an improvement of CIPN-related sensory symptoms. Thus, OnLife® may reduce the severity of existing CIPN in breast cancer patients treated with paclitaxel and thus appears to be a promising treatment option for CIPN.

METHODS

Study Goal and Design

The prospective, multicenter, observational study STEFANO was designed to evaluate the potential of OnLife® to improve existing CIPN in 150 adult patients with colon or breast cancer after neo-/adjuvant CTx (cohort A: colon cancer, oxaliplatin-based therapy, 75 patients; cohort B: breast cancer, paclitaxel therapy, 75 patients) from about 20 sites in Germany (**Fig. 1**).

In-/Exclusion Criteria

Key inclusion criteria:

- Adult patients with colon or breast cancer that have finished neo-/adjuvant oxaliplatin-based or paclitaxel CTx, respectively
- End of neo-/adjuvant CTx does not date back more than 4 months
- Presence of CIPN grade 1-3 (according to the Common Terminology Criteria for Adverse Events (CTCAE) v4.03)

Key exclusion criteria:

- Presence of sensory and/or motor disturbances due to other neurological diseases prior to start of neo-/adjuvant CTx
- Alcohol abuse

Study Treatment and Procedures

A three-month OnLife® treatment with the following daily dosing regimen was recommended: 1-0-1 (p.o., 2 tablets/day, one tablet every 12 hours). Observation included one further month upon discontinuation of OnLife® (**Fig. 1**).

Severity of peripheral sensory and motor neuropathy according to CTCAE v4.03 was evaluated by the treating physician with the help of the following neuropathy assessments:

- **Anamnestic evaluation**
- Measurement of **vibration sensitivity** using a Rydel-Seiffer tuning fork
- Measurement of **deep tendon reflexes** (Patellar and Achilles)

In addition, **patient-reported symptoms and functional limitations** related to CIPN were assessed with the EORTC QLQ-CIPN20 questionnaire.

All assessments were scheduled before start of OnLife® treatment (baseline), after month 1, 2 and 3 after start of treatment (visit 1, 2 and 3) and one month after discontinuation of OnLife® treatment (final assessment) (**Fig. 1**).

Objectives and Endpoints

The main objective of the STEFANO study was to evaluate the effectiveness of OnLife® in improving signs and symptoms of CIPN assessed by the comparison of severity of sensory and motor neuropathy before (baseline), during (visit 1, 2) and at the end of OnLife® treatment (visit 3).

Key analyses to assess effectiveness were:

(1) Changes by at least one CTCAE grade (visit 3 vs baseline)

(2) Sustained improvement (defined as reduction of at least one CTCAE grade at visit 2 and 3 compared to baseline)

Further, vibration sensitivity and deep tendon reflexes were evaluated, and patient-reported outcomes in CIPN were assessed with the EORTC QLQ-CIPN20 questionnaire.

RESULTS

Here, data with focus on sensory paclitaxel-induced CIPN of breast cancer patients are shown. In total, 75 patients with breast cancer after neo-/adjuvant paclitaxel therapy were included. Median age was 61.0 years. The median cumulative paclitaxel dose was 880.3 mg/m². For further details refer to **Tab. 1**.

74 patients presented with grade 1-3 sensory CIPN (CTCAE) at baseline.

(1) Of those, 31% (n=23) patients had an improvement of sensory CIPN, 54% (n=40) experienced a stabilization with no further worthening, 1% (n=1) had a deterioration and 14% (n=10) of patients were not evaluable (**Fig. 2**). In patients with grade 2/3 sensory CIPN at baseline (n=58), 36% (n=21) had an improvement, 50% (n=29) had a stabilization and no deterioration occurred. 14% (n=8) of patients were not evaluable (**Fig. 3**).

(2) Of those, 22% (n=16) patients showed a sustained improvement, experienced already after one month of OnLife® treatment in 56.3% (n=9) of patients.

Improved vibration sensitivity was seen in 40% (n=30) of all patients (n=75), 15% (n=11) had no change. For 17% (n=13) of patients a deterioration was reported, and 28% (n=21) of patients were not evaluable. OnLife® treatment had no mayor effect on deep tendon reflexes (improvement: 20% (n=15), no change: 43% (n=32), deterioration: 16% (n=12), not evaluable: 21% (n=16)).

According to patient-reported outcomes (EORTC QLQ-CIPN20), sensory symptoms improved continuously from baseline to visit 3 (end of treatment with OnLife®), represented by a decrease of the mean sensory scale score of 16.0 points in patients with grade 1 sensory CIPN at baseline and by 13.6 points in patients with grade 2/3 sensory CIPN at baseline, respectively. Upon discontinuation of OnLife® (final assessment) the mean score remained stable in all patients (**Fig. 4**).

45% (n=34) of patients reported less symptoms and functional limitations related to sensory CIPN after OnLife® treatment (visit 3 vs baseline). 20% (n=15) of patients reported no change, 5% (n=4) reported a deterioration, and 29% (n=22) were not evaluable (**Fig. 5**).

Abbrevations:
CIPN: Chemotherapy-induced peripheral neuropathy | CTCAE: Common Terminology Criteria for Adverse Events | CTx: Chemotherapy | EORTC: European Organization for Research and Treatment | FAG®: Fatty Acids Group | p.o.: per os | PEA: Palmitoylethanolamide | PRO: Patient-Reported Outcome | PUFA: Polyunsaturated Fatty Acids | QLQ: Quality of Life Questionnaire | vs: versus

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Conflicts of Interest:
Zaiss: Honoraria: Roche, Pfizer; Consulting or Advisory Role: Roche, Janssen, Celgene, BMS, Astra Zeneca

Uhlig: Consulting or Advisory Role: Roche, Celgene, Janssen-Cilag

Decker: Honoraria: Novartis; Consulting or Advisory Role: Novartis, Celgene

Lehmann: Honoraria: Takeda, CSL Behring, Grifols, Alnylam; Consulting or Advisory Role: Takeda, CSL Behring, Grifols, Alnylam; Research Funding: Sanofi Genzyme

Marschner: Leadership: iOMEDICO; Research Funding: Swiss Medical Food AG

Acknowledgements:
The STEFANO trial was financially supported by Swiss Medical Food AG.

34. Deutscher Krebskongress 2020
19. - 22. Februar 2020, Berlin
Poster-ID: 405

Figure 1

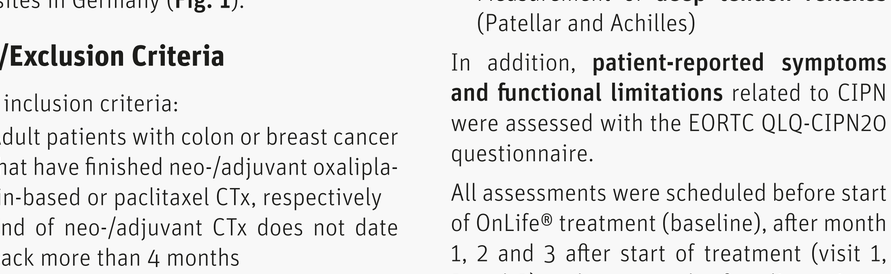


Figure 1 – Study Design

Table 1

Characteristic	N=75
Age, years	
Median, Range	61.0, 37.9-86.0
Gender, n (%)	
Female	73 (97.3)
Male	2 (2.7)
ECOG Performance Status, n (%)	
0	38 (50.7)
1	32 (42.7)
2	4 (5.3)
Missing	1 (1.3)

Characteristic	N=75
Cumulative dose of paclitaxel [mg/m²]*	
Median	880.3
Range	152.6-1080.0
Dose intensity of paclitaxel [mg/m² per week]*	
Median	78.1
Range	18.4-165.5
Severity of sensory CIPN by CTCAE grade, n (%)	
0	1 (1.3)
1	16 (21.3)
2	54 (72.0)
3	4 (5.3)

*Three patients were not included in this analysis since data on prior neo-/adjuvant CTx were not available. ECOG, Eastern Cooperative Oncology Group

Table 1 – Patient demographic and clinical characteristics

Figure 2

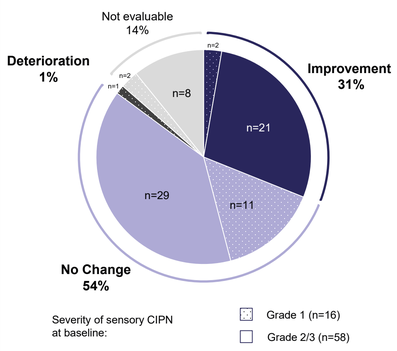


Figure 2 – Changes of sensory CIPN by at least one CTCAE grade in all patients with sensory CIPN at baseline (N=74)

Figure 3

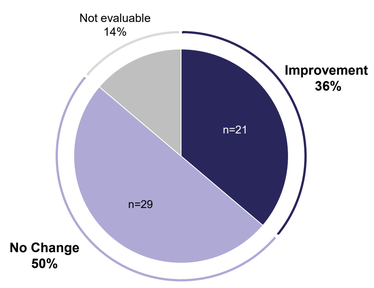
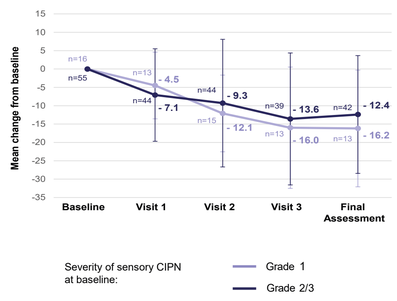


Figure 3 – Changes of sensory CIPN by at least one CTCAE grade in all patients with grade 2/3 sensory CIPN at baseline (N=58)

Figure 4



Lower values indicate less severe symptoms.

Figure 4 – Patient-reported outcomes: EORTC QLQ-CIPN20, Change from baseline in sensory scale (mean, standard deviation)

Figure 5

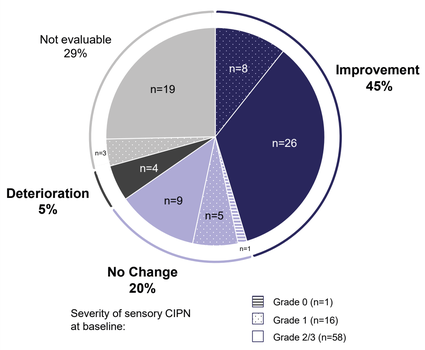


Figure 5 – Patient-reported outcomes: EORTC QLQ-CIPN20, Change in sensory scale in all patients (N=75)