

## Palmitoylethanolamide: A Useful Adjunct in Chemotherapy Providing Analgesia and Neuroprotection

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Dose limiting side effects in chemotherapy are a *crux medicorum*. Targeted cytoprotection such as protection against neurotoxicity and ototoxicity is much sought after. In 2011 the group of Professor Cruccu of the University of Rome, published the results of a clinical trial in 20 patients, showing that the natural compound Palmitoylethanolamide (PEA) administered concomitantly to thalidomide and bortezomib could reduce neuropathic pain after chemotherapy and restore the disturbed neurophysiology of nerves [1]. These results support the notion of targeted cytoprotection during chemotherapy. PEA is widely available as a food supplement (a.o. PeaPure) and has been documented to be a safe and effective analgesic and anti-inflammatory compound based on a number of placebo-controlled clinical trials in thousands of patients [2,3]. This compound therefore could play a valuable role in the field of cancer treatment.

### Protection of Thalidomide and Bortezomib Induced Side Effects

The combination of thalidomide and bortezomib nearly always induces a reversible length-dependent sensory-motor, predominantly axonal, large-fiber polyneuropathy. In a subset of patients, more severe demyelinating polyneuropathy may also develop [4]. Although peripheral length-dependent sensory painful axonal neuropathy is most often found, small-fibre neuropathy also has been documented as a side effect, especially related to the emergence of neuropathic pain [5]. For bortezomib alone, peripheral neuropathy is a significant dose-limiting toxicity that typically occurs directly within the first courses of bortezomib. This adverse event is one of the most significant non-hematologic toxicities of bortezomib, and often leads to dose reductions. While the polyneuropathy is often reversible after bortezomib treatment, thalidomide polyneuropathy seems to be more of a clinical problem as it appears much less reversible. The overall cumulative peripheral neuropathy incidence rate for the combination of both drugs is significant, with reports of approximately 60% over time [6]. For both drugs the emergence of painful neuropathy creates a difficult problem for the oncologist. New treatment options of this dose limiting side-effect will therefore are very much welcomed.

Patients suffering from Morbus Kahler, multiple myeloma, were undergoing a treatment protocol consisting of bortezomib (1.3 mg/m<sup>2</sup> twice a week) and thalidomide (50-200 mg daily), and clear signs and symptoms of neuropathy and neuropathic pain were present in all patients. During the course of the trial no patients interrupted the treatment with bortezomib and thalidomide and PEA was added to the cytostatic regime during 2 months. Clinical signs and neurophysiological measures were taken before and after the concomitant PEA treatment. After 2 months pain was significantly reduced and blinded examiners found that all neurophysiological measures (LEPs, SNAPs, and CMAPs) were significantly improved. These results lead the investigators to suggest that PEA may represent an innovative therapy for patients suffering from chemotherapy-induced painful neuropathy, to obtain pain relief as well as to restore myelinated-fibre function without increasing the toxic effects the patients were already experiencing.

### Protection against Side-Effects of Other Cytostatics

The idea that PEA is able to reduce side-effects of chemotherapy has been brought forward already in a paper from 1975 where results of several experiments in leukemic rats were described [7]. PEA reduced the dose limiting side effects of various combinations of cisplatin vincristine, cyclophosphamide and methotrexate. The dose of chemotherapy could be increased due to the cytoprotective effects of PEA. There was significantly less mortality due to side effects in the PEA treated groups compared to the groups treated with chemotherapy only. The authors thus showed a clear add-on effect of PEA; PEA had positive impact on the survival time after the emergence of the cancer. Survival time of leukemic rats treated with the combination of cisplatin and methotrexate doubled.

The results of both papers have great value for oncologists; PEA may not only reduce polyneuropathic damage during and after chemotherapy, it may also enable oncologists to dose higher or longer in critical situations, and enhance the efficacy and safety of chemotherapy.

### PEA and Its Intrinsic Anti-Tumor Activity

In addition to this, there is quite some evidence to support cytostatic properties of PEA in cancer models. PEA and related signalling lipids are increasingly recognized as playing an important role in down regulating cancer growth [8]. In a melanoma model the anti-proliferative action of a pharmacological intervention was associated with an elevation of PEA levels and larger necrotic regions in the tumor [9]. In a model based on human breast cancer cells PEA potently enhances the anti-proliferative effects of other endogenous lipids [10]. One of the mechanisms through which PEA exerts its anti-proliferative effect might be the TRPV1 receptors [11]. In addition to that NF- $\kappa$ B, a molecular target of PEA, which can be down regulated by PEA, seems to play a distinct role in cancer cells and in inflammatory cells. In inflammatory cells NF- $\kappa$ B activates genes that encode pro-inflammatory cytokines which contribute to tumorigenesis [12]. Inactivation of NF- $\kappa$ B can also reduce chemo resistance and radio resistance of cancer cells. Recently, NF- $\kappa$ B inhibition in combination with cytotoxic drugs and/or irradiation has been pointed out to represent a very promising strategy for cancer therapy and PEA is as we know a NF- $\kappa$ B inhibitor [13].

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The data discussed above support the use of PEA as a part of a chemotherapeutic treatment regime due to its intrinsic tumorostatic, neuroprotective and analgesic properties [14]. Furthermore, PEA seems to be free of negative drug-drug interactions and its safety and tolerability up to a dose of 100 mg/ kg bodyweight/day has been documented [15]. As this compound has a remarkable history of safety and efficacy, since its first description in 1957, its use in the clinic should be considered more often [16].

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