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Artemisia Annua

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Introduction

Artemisia annua is a plant that belongs to the family of Asteraceae and contains Artemisinin, a molecule known for its anti-parasitic properties [1]. Artemisinin is a sesquiterpene lactone with a 1,2,4-tiroxane ring system, used for treating fevers for over two millennia [1]. More recently Artemisia has come to the fore for its antineoplastic potential [2]. Its specific anti-cancer effects have been demonstrated in some research studies and Artemisia's cytotoxic action on different cell lines is described in several scientific works [2,4]. Artemisia's major antineoplastic action appears to be due to the 2EF1 tyrosine kinase enzyme cascade leading to cell death. These studies have raised diffuse interest due to potential clinical applications.

The natural compound extracted from *Artemisia annua* is metabolized in a very short period of time: after an average of 2 hours (between 1½ and 4 hours artemisinin molecules lose their efficacy [4-11]. In the light of these results, more trials have been conducted to obtain an active extract with a longer half-life and some semi-synthetic molecules have been developed having similar mechanisms of action and longer stability [5,6]. The significant antitumoral activity of artemisinin and licensed semisynthetic its derivatives has been documented in *vivo*. One study that tested 55 cell lines from Developmental Therapeutics program of the national Cancer Institute (NCI) showed inhibitory activity against many cancer cells [3]. The Artemisinin and semisynthetic derivatives have much anticancer action: induce cell growth arrest in all cell cycle phase (-7-3); proapoptotic effect by Bax/Bcl-2 gene interaction [7-10]; inhibition metastasis/invasion by MMP gene family and E cadherin activity [11]; angiogenesis inhibition by modulating VEGF, FGF receptors [12-14], also its activity in resistant cancer cells [3-15]. The first in-vivo data about the use of artemisinin in animal models were presented in 2007, but the results previously obtained *in vitro* could not be confirmed. This study demonstrates the dose-depending toxicity of plant [16-17]. Some clinical applications were then tested on human patients treated with hydro-alcoholic extracts in liquid solution, or capsules containing dried extracts at fixed titrations which all showed a weak action, especially with artemisinin derivates, where reported also the side effects of its use [18]. Some anecdotal reports about cases of "miracle healing" have aroused in Italy a growing interest in the do-it-yourself use of this substance.

This lead to the design of an observational study intended to collect the results of the controlled administration of standardized doses of the natural molecule.

21 patients were observed with cancer metastatic progression from primary colon, breast and lung diseases or other progressing lympho-proliferative conditions. All the patients were confirmed as non-responders to standard therapy and all were given *Artemisia annua* in the form of 65% hydro-alcoholic solution or tablets with 95% dried extracts at the dose of 100 and 200 mg. In none of the 21 patients examined did the disease improve or disappear. The same patients were also studied to check any possible effect on the neoplastic lesions (decreased spread and/or volume of the neoplasm), impact on Quality of Life (weakness, state of wellbeing); duration of survival, improvement of haematological parameters. The patients were followed for 4 months up to disease progression confirmed with instrumental and blood tests. In 82% of the patients the disease progressed from the very first month of administration, while the remaining 18% were relatively stable up to the end of the trial. One case of mild regression was reported in a subcutaneous lesion. 50% of the patients experienced a reduction of painful symptoms (with consequent reduction of the use of opioids). Many patients during the treatment have had some side effects, which began with the start of treatment and were interrupted with the discontinuation of the integrator. The side effects include: nausea and vomiting, fever (high in some cases), tremors, increased transaminase, creatinine and blood urea levels, visual hallucinations: side effects were often present all at the same time. All the patients had previously been exposed to at least one anti-blastic treatment, sometimes to more than 3. The side effects mentioned above appeared in the subjects treated with the combination of Artemisinin hydro-alcoholic extracts plus capsules.

All the instrumental and blood tests reported were conducted in different laboratories according to independent and non-standardized protocols.

These observations seem to prove that the two natural extracts of *Artemisia annua* have a weak action on neoplastic lesions. Further studies should be carried out with some semi-synthetic formulas to improve the treatment impact on survival. Extreme caution is to be recommended in the use of *Artemisia annua* especially in the patients already exposed to multiple therapies, due to the risk of severe side effects which might further compromise a generally poor quality of life.

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