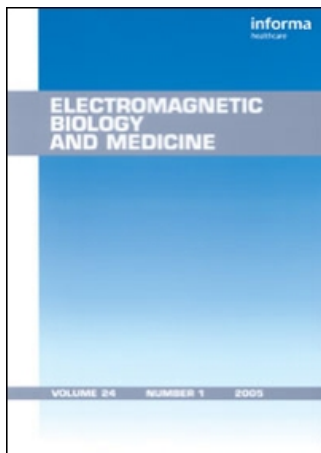


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Extremely Low Frequency Electromagnetic Fields Prevents Chemotherapy Induced Myelotoxicity

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Side effects of chemo-radiotherapy reduce the quality and also the survivability of patients. The consequent fatigue and infections, related to myelodepression, act to reduce the dose-intensity of the protocol. Late side effects of chemo-radiotherapy include secondary tumors, acute myeloid leukemias and cardiotoxicity. Side effects of chemotherapy are related to oxidative stress produced by the treatment. Oxidative stress also reduces the efficacy of the treatment. Antioxidative treatment with natural (dietetic) or chemical agents has been reported to reduce the toxicity of chemo-radiotherapy and improve the efficacy of treatment. We here report our experience with SEQEX, an electromedical device that generates Extremely Low Frequency ElectroMagnetic Fields (ELF-EMF) to produce endogenic cyclotron ionic resonance, to reduce myelotoxicity consequent to ABVD protocol in patients with Hodgkin's lymphoma.

Keywords Antioxidative treatment; Chemo-radiotherapy; Hodgkin's lymphoma; Ion cyclotron resonance; Myelotoxicity.

Introduction

In Hodgkin's and non-Hodgkin's Lymphoma chemotherapy may cure a high number of patients. Improvement of survival reveal tardive toxicity related to chemotherapy and radiotherapy which may appear also within a few decades after conclusion of treatment. Recently Dutch researchers (Aleman et al., 2003) compared the causes of death of over 1,200 patients with Hodgkin's lymphoma with the normal population. They concluded that patients with Hodgkin's lymphoma were at risk of excess deaths from secondary cancers and cardiovascular disease throughout

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more than 30 years of follow-up. They estimated that the rate of death from all causes other than HD was 6.8 times that of the general population.

Chemotherapy also induces a transient toxicity which may present during the treatment and results in fatigue, impairment of the quality of life and myelodepression. In particular myelodepression may reduce the dose-intensity schedule, which may compromise the results of the treatment, requiring supportive treatment with hematological growth-factors. It has been reported (Conklin, 2000; Myers, 1998) that the "oxidative stress" consequent to treatment with chemotherapy and radiotherapy is one of the factors responsible for chemo-radiotherapy-related-toxicity. Oxidative stress is the condition where "reactive oxygen species" (ROS) that are created exceed the capacity of the anti-oxidant system to reduce them. The consequence is an excess of ROS in cells and tissues. Toxicity of chemotherapy is, at least in part, consequent to the production of ROS. ROS are responsible of the mutagenesis induced by chemotherapy, which is one of its late side effects (secondary tumor) (Martingale et al., 2002). Exposure of cellular DNA to ROS induce accumulation of mutations whose end product is tumor production. Anti-oxidative drugs such as amiphostine, dexraroaxane and trimetazidina are used to reduce the toxicity of chemotherapy in particular cardio toxicity (Mantovani et al., 2002; Pascale et al., 2002; Sparano, 1998).

Oxidative stress reduces the efficacy of many chemotherapeutic drugs because it inhibits apoptosis, which is the therapeutic pathway of cell death of tumor cells induced by chemotherapy (Kagan et al., 2002; Shacter et al., 2000). Anti-oxidants on the other hand may improve the efficacy of chemotherapy. Multiple dietary antioxidants and glutamine are efficacious not only to reduce the toxicity of chemotherapy but also to improve its efficacy (Prasad, 2004; Savarese et al., 2003).

SEQEX is an electromedical apparatus which is able to produce 30 different shapes of electromagnetic waves with intensities between 1 to 100 μ T and a frequency between 1 to 100 Hz (Extremely Low frequency ElectroMagnetic Fields [ELF-EMF]). The shape, intensity and frequency of waves are selected by SEQEX on the basis of the measurement of the impedance measured in the body of the subject under treatment. In fact the body of the subject responds to every singular wave received with a cellular ionic movement (endogenous cyclotron ion resonance) measured by changes in body impedance, and the waves which produces better ionic movement are selected and saved in a memory card. Subsequently the waves selected, stored digitally on this card, are used to treat the patient.

Recently Raggi et al. (in press) in work yet to be published reported experimental data, conducted with SEQEX at Perugia University, clearly demonstrating that this treatment is able to reduce oxidative stress in a population of normal people.

These results prompted us: (1) to confirm the data about the potential for SEQEX to reduce oxidative stress and (2) to investigate this property to reduce the toxicity of ABVD chemotherapy. Typical dosages for one 28-day cycle of ABVD are as follows

Adriamycin 25 mg/m² IV on days 1 and 15

Bleomycin 10 mg/m² IV on days 1 and 15

Vinblastine 6 mg/m² IV on days 1 and 15

Dacarbazine 375 mg/m² IV on days 1 and 15

The total number of cycles given depends upon the stage of the disease.

Our experimental design followed 18 patients receiving chemotherapy. Included were nine patients in Group 1 receiving ELF-EMF therapy, and nine patients in Group 2 not receiving ELF-EMF therapy.

Results

(1) We evaluated oxidative stress before and after 27 minutes of 38 SEQEX treatments using the FRAS-3 technique (Cornelli et al., 2001). Overall, the mean oxidative stress was 208.6 at the beginning of treatment and 168.5 at the end, as shown in Fig. 1. We also observed reductions of oxidative stress during the treatment in the majority of tests.

(2) An appropriate dose-intensity of drugs, in accordance with protocol, consists of obtaining maximal efficacy of treatment, measured in terms of percentage and duration of complete remission. In ABVD protocol the major obstacle to prescribing the administration of a correct dose-intensity of drugs is myelotoxicity. The administration of G-CSF attempts to overcome this possible complication. We calculated the dose of G-CSF to administer to patients on the basis of number of neutrophil count checked weekly during chemotherapy.

The median total dose of G-CSF administered during the first four courses of therapy to the patients of Group 1 receiving ELF-EMF treatment was 1200mcg (range: 900–3900mcg) while it was 5100mcg (range: 1200–7500mcg) for the patients of Group 2, the difference is statistically significant ($p = 0.0002$). Usually patients during treatment with ABVD complain of “fatigue”. Fatigue is related to the reduction of haemoglobin levels during chemotherapy and it is one of the causes responsible for the poor quality of life of such patients. We studied the difference between the haemoglobin value (Hb) at the beginning of therapy and the lower value during the four courses of chemotherapy. The median value of Hb reduction in Group 1 was 0.3g/dl (range: 0–1.8g/dl) while in Group 2 it was 1.4g/dl (range: 0–3.2g/dl) (not statistically significant, $p = 0.1$). These clinical data for the 18 patients, the G-CSF administered to each patient and the maximal reduction of Hb levels are reported in Table 1.

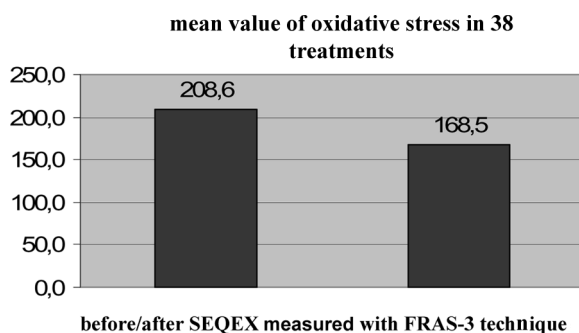


Figure 1. Evaluation of oxidative stress before and after 27 minutes of 38 SEQEX treatments as measured using the FRAS-3 technique.

Table 1

Patients 1 to 9 had supportive therapy with Seqex. Patients 10 to 18 in the second group did not. Age and stage are similar in the two groups. The G-CSF administered in the two groups is statistically different and is greater for those who did not receive the Seqex treatment. The group of patients not receiving the supportive treatment tended to have a larger decrease of haemoglobin, but this decrease was not statistically significant

Group	Age	Sex	Stage	G-CSF (μg) administered	Major Hb reduction (g/dl)
N° 1	42	F	II A	1200	0.9
N° 2	44	M	III A	1500	1.8
N° 3	45	M	II A	900	0
N° 4	69	M	I A	3900	0
N° 5	38	M	III A	1200	1.5
N° 6	35	F	II A	1200	0.5
N° 7	26	F	II A	1200	0.1
N° 8	39	F	III A	1200	0
N° 9	40	F	IV A	2400	0.6
Mean	40			1200	0.3
N° 10	47	F	III A	5100	3.2
N° 11	26	F	II A	5700	0.4
N° 12	20	M	III A	3600	0
N° 13	27	F	II A	1200	1.2
N° 14	78	F	II A	7500	2.7
N° 15	26	M	III A	4800	1.4
N° 16	40	M	II A	6600	1.6
N° 17	23	F	II A	5100	0
N° 18	43	M	I A	4500	1.6
Mean	27			5100	1.4

Conclusion

SEQEX through its production of selective ELF-EMF signals is able to reduce the oxidative stress. This may reduce the side effects of chemotherapy, specifically myelodepression. We know that oxidative stress may be, at least in part, responsible for secondary malignancies and cardiovascular diseases consequent to radio-chemotherapy, so we conclude that this medical device which reduces oxidative stress induced by treatment with chemo-radiotherapy may reduce the risk of these late toxicities.

We also conclude that the use of SEQEX in combination with a diet rich in anti-oxidant agents may further improve these results. We are involved in ongoing studies to find a protocol to prove the efficacy of such association as a supportive treatment for patients with Hodgkin and non-Hodgkin disease who are candidates for chemotherapy.

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