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Editorial Comment

Mistletoe for cancer?

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In this issue of the *European Journal of Cancer* (pp. 23–31, Steuer-Vogt and colleagues present a randomised multicentre trial of a standardised mistletoe extract used as an adjuvant therapy for patients with resected head and neck cancer [1]. They enrolled almost 500 patients and followed them for an average of 4 years. Their results show no advantages in terms of survival for mistletoe plus standard treatment over standard treatment alone. Why is this study (as I believe) important?

Complementary/alternative medicine (CAM) has become an important topic for oncologists. The obvious reason for this is that more and more cancer patients seem to try one form of CAM or another. A systematic review of 26 surveys from 13 countries [2] suggested that approximately one-third of all cancer patients try CAM. The most commonly employed therapies include herbs, homoeopathy and relaxation treatments. The reasons for this high level of popularity are intuitively obvious to most of us. Morant and colleagues [3] investigated them in some detail and found that many cancer patients feel compelled to try CAM because they want to 'leave no stone unturned' in their search for a cure, they feel that using the mind might help the body, they are impressed with positive reports about CAM which regularly appear in the media, they prefer a holistic approach to cancer therapy, and they are led to believe that CAM is free from adverse side-effects and risks. It would be easy to falsify most of the assumptions that underlie such notions, but perhaps it is kinder towards our patients to respect their beliefs and offer skilled guidance through the confusing jungle of CAM options.

Such guidance, one might hope, is provided in the plethora of books on CAM. However, a quick glance at three [4–6] such volumes (chosen at random) gives sobering insights. The range of treatment modalities (Table 1) that is being recommended for CAM is staggering, some might say misguided. Evidence and opinion are often at variance in medicine; it seems, however, that this is particularly true in CAM for cancer. Evaluating the facts according to the principles for evidence-based medicine (E. Ernst, University of Exeter, Exeter), I found no compellingly positive data for any form of CAM (Table 2).

This statement also includes mistletoe (*Viscum album*). If CAM for cancer is a controversial and emotive issue, mistletoe therapy for cancer is a veritable minefield. The mistletoe story apparently dates back to Celtic druids who treasured the medicinal properties of the plant and used it as a panacea. Hippocrates and early Arabian physicians used it for epilepsy, heart disease, oedema and diseases of the spleen [7]. Based on the intuitions of Rudolf Steiner (1861–1925), mistletoe became an anthroposophical medicine for cancer in the early part of the last century [8]. Since then much research has been devoted to identifying its constituents and verifying their anticancer properties. Like many other plants, mistletoe does activate the immune system which could *potentially* translate into valuable clinical effects [9]. One problem with (some of) this evidence is that authors tend to jump to conclusions which are not supported by their data. For instance, one *in vitro* study concluded that mistletoe "may modulate the system of immune surveillance and recognition in patients under mistletoe therapy" [10]. The authors of another *in vitro* investigation conclude that "mistletoe leukin-1 can be recommended for the adjuvant treatment of cancer

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patients'' [11]. To extrapolate from *in vitro* results to the much more complex clinical situation is, it seems to me, naïve at best and irresponsible at worst.

The ultimate question, therefore is, do mistletoe extracts benefit cancer patients? It is easy to find euphemistically positive answers to this question in the recent literature: ''some 50 clinical studies report extended survival times, improved quality of life or, in some studies, tumour regression with mistletoe therapy'' [7]. Such optimistic statements are often based on an analysis [12] which included studies with severe (often fatal) flaws and which is, therefore, far from convincing.

Two serious attempts to evaluate mistletoe therapy come to considerably less enthusiastic verdicts. Kleijnen and Knipschild [13] published a systematic review of all 11 controlled clinical trials available in 1994. They found that the average quality of these studies was poor. The majority of these data suggested some benefit, but the only rigorous study turned out to be negative. The authors concluded: ''we can not recommend the use of mistletoe extracts in the treatment of cancer patients with an exception for patients involved in clinical trials'' [13]. More recently, the ''Canadian Breast Cancer Research Initiative'' assessed the totality of the preclinical and clinical evidence. The conclusion was similarly reserved: ''the evidence of clinical benefit from human studies remains weak and inconclusive'' [14]. Now several new trials are emerging. A placebo-controlled trial of Lektinol® (a pure lectin preparation) with 272 patients suffering from breast cancer seems (according to an aggressive advertising campaign by the manufacturer) to show an improvement of quality of life. A further study with melanoma patients seems to have been negative [15]. To judge either of these trials is premature; and we must obviously wait until the full publications of these results become available.

This brings us back to the trial published in this issue. Conducting clinical trials in this area is often the art of the humanly possible rather than the theoretically desirable, and no clinical trial can ever be entirely free from shortcomings. The study by Steuer-Vogt and colleagues [1] is probably no exception. Yet, overall, the study is sound and clearly belongs to the most rigorous trials on this subject. The authors should certainly be applauded for conducting the trial and for publishing a negative result. Will the disappointingly negative findings of their study end the emotional debate about mistletoe? I do not think so. Proponents of mistletoe will

Table 1
Full list of complementary/alternative medicine (CAM) therapies positively reviewed in three recent CAM books

714X therapy	Immunoaugmentative therapy
Acupuncture (2)	Juice therapy
Antineoblaston therapy (2)	Mangosteem peel
Antioxidants	Meditation (2)
Antrodia cinnamomea	Melatonin (2)
Ayurvedic medicine (2)	Mind–body therapies (2)
Bioelectromagnetic therapy (2)	Naturopathy
Biofeedback	*Panax ginseng*
Capsicum	Pancreatic enzyme therapy
Carotenoids	Phyto-oestrogens
Cell-specific cancer therapy 200	Pomegranate leaf
Chinese medicine	*Pteris multifida poir*
Co-enzyme Q10	*Pulsatilla chinensis*
Coley's toxins	Qi gong
Coriolus versiculor	Relaxation
Dance therapy	Selenium
Detoxification therapy	Shark cartilage
DHEA	Social support
Diet (2)	Spirituality
Evening primrose oil	Tricosanthes
Garlic	Vitamin A
Green algae	Vitamin C
Green tea	Vitamin E
Guar leaf	
Guided imagery	
Homoeopathy	
Hydrazine sulphate (2)	
Hypnotherapy	

Numbers in brackets indicate frequency of mention (no number means treatment was only mentioned in one of the three books). Data from Refs. [4–6]. DHEA, dehydroepiandrosterone sulphate.

Table 2
Complementary/alternative medicine (CAM) therapies for cancer assessed using an evidence-based approach

CAM therapy	Direction of evidence
Cancer prevention	
Allium vegetables (e.g. garlic)	Highly encouraging
Green tea	Encouraging
Panax ginseng	Highly encouraging
Vegetarian diet	Ambiguous
Cancer treatment	
714X	Negative
Aloe vera	Encouraging
Di Bella therapy	Negative
Essiac	Ambiguous
Gerson diet	Not convincing
Hydralazine sulphate	Encouraging
Laetrile	Negative
Macrobiotic diet	Negative
Melatonin	Encouraging
Mistletoe	Ambiguous
Shark cartilage	Negative
Sho-saiko-to	Encouraging
St John's wort	Encouraging
Support groups	Encouraging
Thymus extracts	Ambiguous
Palliative care	
Acupuncture	Encouraging
Biofeedback	Encouraging
Enzyme therapy	Encouraging
Hypnotherapy	Encouraging
Massage	Encouraging
Melatonin	Encouraging
Music therapy	Encouraging
Relaxation	Highly encouraging
Therapeutic touch	Encouraging

Table 3
Safety of mistletoe

Alleged adverse side-effects and complications	Alleged interactions with
Allergic reactions (including anaphylaxis)	Antihypertensives
Ascites	Cardiac drugs
Bradycardia	CNS depressants
Cardiac arrest	Immunosuppressants
Coma	
Congested intestine	
Death	
Dehydration	
Delirium	
Diarrhoea	
Gastroenteritis	
Hallucinations	
Headache	
Hepatitis	
Hypotension	
Leucocytosis	
Local irritation (at injection site)	
Muscle contracture	
Mydriasis	
Myosis/myalgia	
Nausea	
Negative-inotropic effect	
Pancreatic haemorrhage	
Pyrexia	
Seizures	
Vomiting	

Data from Refs. [16,17].

point out that its negative result applies only to the experimental conditions of this particular study. Other types of cancer might respond differently and other mistletoe preparations or treatment regimens could still yield a benefit. There are dozens of further 'ifs' and 'buts'. It is, therefore, unlikely that this study will deter many cancer patients from experimenting with mistletoe.

And why should they be deterred? After all, there is little evidence that the therapy is associated with serious risks! Or is there? Contrary to what proponents want us to believe, there are several reports of adverse side-effects and serious complications (Table 3) after mistletoe therapy [16,17]. Moreover, any ineffective CAM therapy can do harm when it is used as a true alternative to conventional treatments. Harm can also be caused through the expense of mistletoe preparations — the money might be used elsewhere with greater benefit to the patient. Raising false hopes in vulnerable people can also be regarded as harmful. After carefully considering this (lack of) evidence I, therefore, conclude that we must determine the truth about the clinical efficacy of mistletoe. Scientific integrity and honesty simply demand this. In the long run, I predict that our patients will thank us for it.

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