Acupuncture: could it become everyday practice in oncology?

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Acupuncture is a complementary and alternative medical treatment (CAM) which is increasingly used in the care of cancer patients. Traditionally derived from Chinese medicine, nowadays it is becoming a part of evidence-based oncology. The use of acupuncture in these patients has been recommended by the American Cancer Society (ACS) for the treatment of side effects associated with conventional cancer therapy and cancer-related ailments. A growing body of evidence supports the use of acupuncture in the treatment of cancer-induced pain and chemotherapy-related nausea and vomiting. Also other indications, such as xerostomia, fatigue, hot flashes, anxiety and peripheral neuropathy, are being constantly evaluated. This article summarizes the most important discoveries related to the possible usefulness of this method in contemporary oncology. Emphasis is placed on the results of randomized controlled trials with an adequate level of evidence. However, explanation of the mechanisms responsible for these effects requires confirmation in further studies with an adequate level of evidence. In future, acupuncture may become an interesting and valuable addition to conventional medicine.

Key words: acupuncture, cancer, complementary and alternative treatment, side effects, supportive treatment.

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Introduction

Complementary and alternative medical treatment (CAM) has gained significant interest in recent years [1]. Although the list of CAM has changed over the years, the Office of Alternative Medicine (established at the National Institutes of Health [NIH] in the USA) nowadays recognizes five major categories [2]. Acupuncture, belonging to the Manipulative Therapies category, due to its low cost, safety (considering all possible contraindications) and the minimal number of side effects is gaining popularity among patients [3]. Acupuncture has repeatedly been reported to be useful in oncological practice in alleviating side effects of anti-tumor treatment. Numerous clinical trials of acupuncture indicate its potential role in fighting the following ailments: nausea and chemotherapy-induced vomiting, pain, xerostomia, vasomotor symptoms, neutropenia, fatigue, anxiety, insomnia, lymphoedema after mastectomy, and peripheral neuropathy [4–16]. A sudden increase in the number of studies on acupuncture in oncology was first noted in 1997, when at the NIH conference a consensus was reached on the use of acupuncture, which was then acknowledged as a useful medical procedure [17]. This article reviews the literature concerning the referred studies.

What is acupuncture?

Acupuncture is a method of treatment that has its origins in Traditional Chinese Medicine and is based on over 4,000 years of empirical evidence. The technique involves the insertion of thin needles into specific locations (energy points) on the patient's body along energy pathways or meridians. According to Chinese philosophy, the hypothetical substance Qi (vital energy) flows in the human body along the meridians, and blockage of Qi leads to a particular ailment [18]. There are 12 main and 8 extra meridians. All the main meridians consist of internal channels connected with the 12 body organs and the external channels spreading symmetrically on the skin surface. The literature describes around 360 energy points located on the external parts of the meridians. Acupuncture is considered to cure diseases by stimulating particular acupoints and removing blockage of Qi [19]. Figures 1–3 present acupuncture meridian pathways.

Although acupuncture has been studied extensively in both animal and human models, little is known about its mechanisms that could explain acupuncture's therapeutic qualities. Table 1 shows suggested mechanisms of acupuncture. This treatment method has been the focus of increased interest, which has resulted in a growing number of studies.

Acupuncture as supportive treatment

Chemotherapy agents are considered to be medications with the most severe side effects, which in many cases may force the patient to abandon therapy. Because of that, proper alleviation of side effects is most crucial. Acupuncture should not be seen as a replacement for modern medicines, but rather an adjunct with a low level of procedure-related complications

that may enhance efficacy and in some cases allow the dosage of other drugs to be reduced. Acupuncture as part of supportive treatment in oncology has been tested for numerous indications. The strongest evidence from a randomized controlled trial (RCT) with low risk of bias supports the use of acupuncture for control of nausea and vomiting related to chemotherapy [25]. This indication seems to be very important, as the high emetogenicity

Table 1. Possible mechanisms of action of acupuncture

Possible mechanisms of action of acupuncture	Effects	References
Local inflammatory response • histamine • prostaglandins • chemokines	• increasing permeability and dilatation of the capillaries • promotion of blood flow to the site • initiation of the migration of phagocytes and signaling them to increase production of various mediators	[20]
Cytokines • decreased expression of IL-6, βNGF and TIMP-1 • reducing proinflammatory cytokines IL-1, IL-6, TNF-α through activation of CB2 receptors	• anti-inflammatory effect • antinociceptive effect on inflammatory pain	[21, 22]
ANS • increasing synchronization between the two branches of the ANS and improvement of HRV	• mediating global physiological regulation	[23]
Stem cells • increasing levels of non-differentiated progenitor of stem cells CD133+ and CD34– cell in the serum of patients after spinal cord injury • promotion of proliferation and differentiation of neural stem cells, up-regulation of the growth factors and the expression of VEGF mRNA in the rats ischemic brain	• spinal cord stem cell mobilization • protection cerebral injuries after ischemia and promotion nerve regeneration	[24]

IL – interleukin; NGF – nerve growth factor; TIMP-1 – tissue inhibitors of metalloproteinase-1; CB2 – cannabinoid receptor 2; ANS – autonomic nervous system; HRV – heart rate variability; CD – cluster of differentiation; VEGF – vascular endothelial growth factor

Table 2. Possible mechanisms of action of acupuncture and its effectiveness in the treatment of various types of ailments related to cancer therapy

Condition	Possible molecular mechanisms of action	Clinical trials	References
	Randomized control trials		
Nausea and chemotherapy-induced vomiting	Multiple mechanisms • influences the endogenous opioid system and changes the serotonin transmission • has effects on the gastric myoelectrical activity • increases vagal modulation • influences the cerebellar vestibular activities	RCT: • acupuncture significantly reduced the number of episodes of emesis between three groups: electroacupuncture, minimal needling and pharmacotherapy alone (median number of episodes, 5, 10, and 15, respectively; $p < 0.001$)	[26]
Cancer pain	Opioid peptides • increased concentration level observed in the serum and brain tissue after acupuncture Neuromodulation • activity modulation of the human brain areas (activated in acute or chronic pain) during acupuncture in neuroimaging (fMRI, PET, EEG)	Meta-analysis of RCTs: • acupuncture did not make a better effect than drug therapy ($n = 886$; RR 1.12; 95% CI: 0.98 to 1.28; $p = 0.09$) • combination therapy (acupuncture with drug therapy) was more effective than drug therapy alone ($n = 437$; RR 1.36; 95% CI: 1.13–1.64; $p = 0.003$)	[7, 8, 27–31]
Chemotherapy-induced leucopoenia	Multiple mechanisms • promotes the release of WBC from bone marrow • prolonging the life of WBC • increases the activity of CSFs • promotes the proliferation of haemopoietic stem cells • reduces haemopoietic stem cells damage by chemotherapy • improves microcirculation	Meta-analysis of RCTs from China: • acupuncture was effective in increasing WBC level • mean difference in the WBC level was 1221 WBC/μl (95% CI: 636–1807, $p < 0.0001$) Pilot study from USA: Significant increase in the median leukocyte value for baseline value after acupuncture ($p = 0.046$): • 8600 WBC/μl, 95% CI: 4800–12000 in the test group • 4400 WBC/μl, 95% CI: 2300–10000 in the control group Decrease in the frequency of occurrence of severe leucopoenia ($p = 0.02$): • 30% in the test group • 90% in the control group	[11, 32–34]

Table 2. *Cont.*

AI-induced arthralgias	Multiple mechanisms • increases the opioid peptides level • improves blood flow	RCT: Significant difference between the test group and the control group at 6 weeks of treatment was observed in: • the mean BPI-SF worst pain scores (on the scale from 0–10, 10 being the most intense pain; 3.0 vs. 5.5; $p < 0.001$) • pain severity (2.6 vs. 4.5; $p = 0.003$) • pain-related interference (2.5 vs. 4.5; $p = 0.002$)	[35]
Radiation-induced xerostomia	Neural transmission: • bilateral activation of the brain function area in fMRI that is responsible for salivary production CGRP: • increase the release of CGRP, which positively affects the salivary flow rates	RCT: In the acupuncture group as compared to the control group was observed: • significant reduction in dry mouth symptoms measured by means of the VAS ($p < 0.05$) • increase in unstimulated and stimulated salivary flow and production ($p < 0.001$)	[9, 36, 37]
Hot flushes	Neuromodulation • increases endorphin release and decrease noradrenalin and serotonin activity in the central nervous system (make thermoregulation more stable) CGRP • direct effect on the release of vasodilator – CGRP in peripheral nerve endings	RCT: Significant reduction of hot flushes and sleep disturbances was observed in: • 16 patients (52%) of the test group • 7 patients (24%) of the control group. • effect was obtained after the second acupuncture session and lasted for the next 12 weeks after treatment	[38, 39]
Anxiety-like behaviour and stress	NPY and CRF • increases NPY mRNA levels and reduces CRF mRNA levels in the amygdala of rats after acupuncture	Randomized controlled experimental study: • after 10 acupuncture sessions patients with generalized anxiety disorders demonstrated significantly reduced anxiety (85.7%) following compared to a placebo group	[13, 40, 41]
		Non RCT studies	
Chemotherapy-induced peripheral neuropathy	Purinergetic signaling • stimulating purinergic signals (increase in the release of adenine nucleotides and adenosine from skin keratinocytes) and neurotransmission in the central and peripheral nervous system	Pilot study: • acupuncture treatment for 6 weeks was effective in 82% ($n = 14$) of patients	[16]
Cancer-related fatigue	• multicomponent	Prospective, clinical study: • significant improvement after 2 weeks of treatment was observed with regard to: general fatigue ($p < 0.001$), physical fatigue ($p = 0.016$), activity ($p = 0.004$) and motivation ($p = 0.024$), and lasted for 2 weeks after the end of the intervention	[12]
CRT-induced dysphagia	Multiple mechanisms • increase the saliva production • restore swallowing reflex • inhibition the fibrosis process	Case series study: • The treatment was effective in: 9/10 patients (90%) of the test group (subjective improvement in the swallowing function, decrease in dry mouth symptoms, pain and fatigue level) • in 6/7 patients (86%) it was possible to remove the PEG tube (a median time of 114 days from the last CRT session and acupuncture treatment, the range from 49 to 368 days)	[42]
Hiccup	Modulation of the hiccup reflex arc • locally: changing blood perfusion, activating the autonomic nervous system, regulating inflammatory mediators • centrally: influences the hiccup center by modulating the secretion of neurotransmitters and neurohormones (endogenous opioids, norepinephrine, serotonin, substance P)	Case series study: After 1–3 courses of treatment (over a 1–7-day period) was observed: • complete symptom relief in 13 patients (81%, $p < 0.0001$); • partial symptom relief in 3 patients (18.8%) • substantial improvement in discomfort ($p < 0.0001$), fatigue ($p = 0.0078$) and anxiety ($p < 0.0001$)	[43]
Lymphoedema	• unclear	Pilot study: After 4 weeks of treatment, 30% reduction of oedema in comparison to the baseline results was observed in 4/9 patients (44.5%)	[15]

RCTs – randomized controlled trials; fMRI – functional magnetic resonance imaging; RR – relative risk; PET – positron emission tomography; EEG – electroencephalography; NPY – neuropeptide Y; CRF – corticotropin-releasing factor; CGRP – calcitonin gene-related peptide; VAS – visual analogue score; CRT – chemoradiation therapy; PEG – percutaneous endoscopic gastrostomy; AI – aromatase inhibitors; BPI-SF – the Brief Pain Inventory – Short Form; WBC – white blood cells; CSFs – colony-stimulating factors

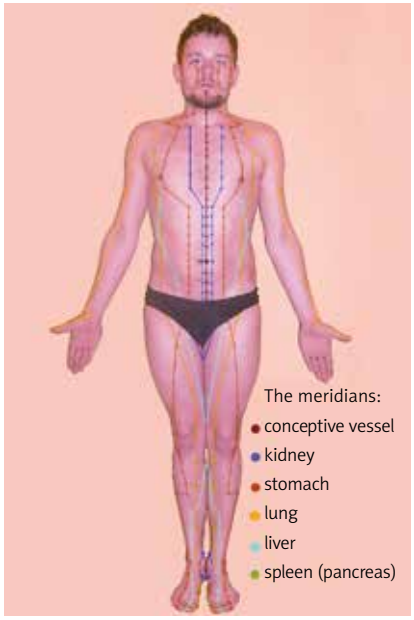

Fig. 1. The course of main meridians on the anterior surface of the body

Fig. 2. The course of main meridians on the posterior surface of the body

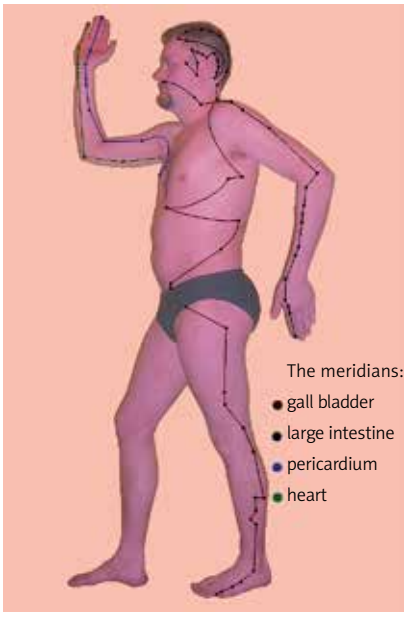

Fig. 3. The course of main meridians on the lateral surface of the body

of many cytostatic agents is hard to control even with three-drug therapy [26]. Despite many RCTs on treatment of other chemotherapy-induced side effects, the level of evidence is not yet satisfactory, but considering its relative safety, acupuncture may be useful in everyday practice. Descriptions of these clinical trials on the effectiveness of acupuncture in minimizing cancer treatment-related side effects are summarized in Table 2.

Level of evidence issue

A recently published systemic review stated that other indications, such as pain, xerostomia, vasomotor symptoms, fatigue, mood disorders, and insomnia, were not evaluated in RCTs with an appropriate level of evidence [44]. One of the major problems with the reviewed studies is their poor methodological quality, mostly difficulty with blinding and a low number of subjects. Also the optimal design of such studies (acupuncture vs placebo, acupuncture vs sham acupuncture) has not been established yet [45]. In spite of satisfactory results in most of these studies, further research on a larger group of patients is necessary.

Summary

In an oncological setting, acupuncture is still being constantly reviewed. Nevertheless, the present available evidence suggests that acupuncture may become a safe, low-cost and efficient form of complementary therapy in modern oncology. The potential role of acupuncture has been found in alleviation of various symptoms, but the data from the majority of clinical studies on acupuncture are heterogeneous. The incomplete description of procedural methodology and insufficient patient groups limit their value. Thus, further research on a larger scale on the potential use of acupuncture in contemporary oncology is required. It should be emphasized that alternative medicine may become the source of a number of interesting concepts worth examining and testing in research and clinical settings.

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