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Review

Thymus Therapy for Cancer? A Criteria-based, Systematic Review

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INTRODUCTION

COMPLEMENTARY OR alternative (the latter term seems far less appropriate) therapies for cancer are highly prevalent [1, 2]. Many different and heterogeneous approaches exist [3]. One mechanism, through which some of these therapies are claimed to work, is the stimulation of the immune system. In the view of proponents of complementary therapies, cancer and/or orthodox cancer treatments are associated with immunosuppression, which in turn reduces the chances of the body fending off the continuous attack by malignant growth. The stimulation of the immune system, it is hoped, will reverse immunological deficits and, therefore, delay the progression of the disease.

The thymus is thought to be a key organ for the development of cell-mediated immunological defense. Thymic hormones are involved in the maturation of T lymphocytes [4]. Drugs prepared from this organ are, therefore, promoted for the (adjuvant) treatment of various forms of cancer. This paper will review the evidence for and against clinical effectiveness of thymus therapy for cancer.

LITERATURE SEARCH

A computerised Medline-search (1966–1996) was conducted (MESH headings: cancer, alternative medicine, thymus extract, cell therapy). In addition, books and non-Medline-listed articles on the subject were searched for references. Several experts in the field were also consulted. All papers thus retrieved were scanned for further relevant references in their bibliographies. Only randomised clinical trials (RCTs) were included in this review. Thirteen such studies were identified. Their methodological details are summarised in Table 1.

A small ($n = 46$), three-armed study tested two different dosages (60 mg/m^2 or 20 mg/m^2 twice weekly for 6 weeks) of thymosin fraction V against no thymosin therapy in 55 patients with lung cancer [5]. All patients were also treated with intensive chemotherapy. The treatment period was 2 years. The results show that thymosin treatment did not increase the complete response rate. Patients on the high-dose thymosin therapy had significantly longer survival time compared to those in the other groups. This was due to prolonged relapse-free survival. The trial is flawed in several ways (Table 1). Most importantly, the sample size was small, and there was no blinding. Therefore, firm conclusions cannot be drawn.

Luzi and associates treated 50 patients suffering from inoperable lung cancers with conventional radiochemotherapy [6]. The experimental group received a standardised thymus extract in addition. The results demonstrated poorer survival rates in the patients thus treated. The authors performed a number of subanalyses according to cancer type. These, however, are post-hoc analyses which cannot infer causality between treatment and outcome.

Schulhof and colleagues studied 42 lung cancer patients treated with two different dosages of thymosin-α1 [7]. Compared to placebo, there were advantages in terms of immunological variables, survival and recurrence-free intervals. Survival rates also favoured the experimental group. However, there was an unevenness of pre-trial surgical interventions that might have biased the clinical outcome. It should also be mentioned that the clinical results were evaluated by post-hoc analyses.

Migeod and coworkers treated patients who, within the last 2 years, had been diagnosed as having breast or colorectal cancers (T2 N0 M0) [8]. Two groups received commercially available thymus organ lysates intramuscularly (i.m.), while the control group received vitamin B complex injections which were thought to represent a placebo. No details as to the treatment schedules and length of therapy were supplied. Similarly, essential details of the statistical methodology were also missing. The results, implying an improved T-cell function in both experimental groups, are, therefore, of questionable validity. No clinical outcome measures were included in this study.

Trutwin and colleagues tested a commercially available oral thymus preparation against placebo [9]. The study group comprised 67 breast cancer patients who had under-

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Table 1. Randomised clinical trends on thymus therapy for cancer

Author [Ref.]	Design	Sample	Intervention	Results	Comment
Cohen and associates [5]	Three parallel groups, open	55 patients with lung cancer	1. 60 mg/m^2 thymosin fraction V 2. 20 mg/m^2 thymosin fraction V 3. No treatment All in addition to chemotherapy twice/weekly for 6 weeks	Patients on high-dose regimen had significantly longer survival times	Small sample size. 9 patients who did not fulfil inclusion criteria were nevertheless randomised. No correction for multiple significance testing.
Luzi and associates [6]	Two parallel groups, open	50 patients with inoperable lung cancer	Experimental group received 0.5 mg/kg thymostimulin daily for 15 days, subsequently weekly for 6 months (in addition to chemotherapy and radiotherapy). Control group: only chemoradiotherapy	6 months mortality: 52% experimental group 28% control group	Sub-analyses are of questionable validity
Schulhof and associates [7]	Three parallel groups, open	42 patients with lung cancer	1. 900 µg/m^2 thymosin-α1 2 × 1 week 2. 900 µg/m^2 thymosin-α1 daily 3. Placebo All in the last week of radiotherapy	Immunological data, survival time and recurrence-free time favoured experimental groups	Survival and recurrence analyses were post-hoc. Uneven distribution of cases with prior surgery. Not double-blind
Migeod [8]	Three parallel groups, single-blind	36 patients with breast or colorectal cancer (T2 N0 M0)	1. 15 mg Neythymun® 2. 15 mg Ney Tumorin® 3. Vitamin B complex as placebo	T-cell function favours groups 1 and 2	Essential details of treatment schedule are missing. Statistical details are lacking.
Trutwin [9]	Two parallel groups, double-blind	67 patients with breast cancer after chemotherapy	1. 3 × 10 Drg Zellmedin Thymus 200®/day 2. Identical placebos	T4/T8 quotient favoured experimental group. Subjective well-being also.	No data on survival etc.
Chisesi [10]	Two parallel groups, open	41 Hodgkin's patients (1A-IV AB) in remission following radiochemotherapy	1 mg/kg thymostimulin 3 times/week for 4 weeks followed by twice weekly for 12–14 weeks	Positive effects on T-cells and on incidence of herpes infections.	Multiple testing. Unclear treatment schedule. No randomisation. No survival data.

Iaffaioli and associates [11]	Two parallel groups, open	51 patients with breast cancer after breast amputation	50 mg/m^2 thymostimulin daily for 2 weeks followed by same dose twice weekly for 3 months in addition to chemotherapy. Controls: only chemotherapy	Less suppression of WBC and platelet count and less infections in experimental group.	No data on tumour progression.
Liberati and associates [12]	Three parallel groups, open	19 Hodgkin's patients in complete remission	1. 50 mg thymostimulin i.m. daily 2. 50 mg thymostimulin i.m. every other day both for 35 days, subsequently, the same dose twice weekly in both groups for 22 weeks 3. No thymostimulin treatment	Improvement in immunological variables.	Sample size too small. No data on tumour progression. Not double-blind.
Macchiarini and associates [13]	Two parallel groups, open	26 patients with small cell lung cancer	Six cycles of chemotherapy with or without thymostimulin followed by maintenance therapy	Less myelosuppression fever and infections in experimental group. Significant improvement in complete responses and survival.	Response and survival rates not necessarily related to thymostimulin. Small sample size.
Canovas-Fernandez and associates [14]	Two parallel groups, open	40 lymphoma/myeloma patients	1. Standard chemotherapy 2. Same with thymostimulin	No inter-group differences in performance status, haematological variables or complications.	No survival data. Small sample size.
Pavesi [15]	Four parallel groups, open	Patients with metastatic breast cancer	Information missing	Less toxicity and better quality of life in experimental group.	Published as abstract only.
Mustacchi and associates [16]	Two parallel groups, open	241 patients with colorectal carcinoma	1. Standard chemotherapy 2. Same with thymostimulin	Significantly more remissions in experimental group (30 versus 18%). Less adverse effects.	Multicentre study. Data imply improved response to chemotherapy.
Frederico and Gobbi [17]	Four parallel groups, open	134 patients with newly diagnosed non-Hodgkin's lymphoma	2 standardised chemotherapy regimen with or without Thymostimulin	Complete remission rate with versus without thymostimulin (59 versus 42%). Four-year survival rates (65 versus 43%).	Survival rates not statistically significant.

i.m., intramuscular.

gone extensive chemotherapy. Both the T4/T8 quotient and patients' well-being favoured the experimental treatment. This study was double-blind, but failed to report on clinical outcomes such as survival or recurrence rates.

Chisesi investigated 41 Hodgkin's patients [10]; all had previously been treated with radiation and some also with chemotherapy. At entry into the trial, all patients were in full remission. The experimental group received thymostimulin for 12–14 weeks. The control group did not receive such adjuvant therapy. The results showed an advantage in terms of recruitment of T cell compartment. Furthermore, there were less herpes infections in the experimental group. No other clinical outcomes, in particular no survival rates, were reported.

Iaffaioli and coworkers treated 51 patients with operated breast cancers either with thymostimulin in addition to chemotherapy or with chemotherapy alone [11]. The experimental therapy was followed by less infections during the follow-up. Blood cells were also less suppressed in the experimental group. Unfortunately, the study provided no information on tumour progression and related clinical data.

Liberati and colleagues studied 19 Hodgkin's patients in remission [12]. They were treated with two different regimens of thymostimulin or placebo. The verum treatments resulted in improved immunological status, but no data on tumour progression or clinical benefit were recorded.

Macchiarini and coworkers treated 26 patients with small cell lung cancer with chemotherapy with or without thymostimulin (1 mg/kg i.m. during days 7–14 of each of the six cycles of chemotherapy) [13]. Complete responders subsequently received a thymostimulin maintenance treatment (1 mg/kg i.m. twice weekly) until relapse. There were less complications in the experimental group. This allowed higher doses of chemotherapy which in turn resulted in a significantly better complete response and survival rate.

Canovas-Fernandez and colleagues studied 40 lymphoma/myeloma patients under chemotherapy [14]. Half received additional thymostimulin. There were no inter-group differences in performance status, haematological parameters, skin reactions or infections.

Pavesi and coworkers conducted a multicentre study of the high-intensity FEC regimen (5-fluorouracil, epirubicin and cyclophosphamide), high-dose folinic acid, and thymostimulin in patients with metastatic breast cancer [15]. 296 patients were randomised to four groups, two of which received thymostimulin. Significantly less haematological toxicity was noted in the patients receiving this drug. Quality of life measurements were enhanced in the thymostimulin groups. However, response rates were not significantly different.

Mustacchi and coleagues reported a multicentre trial of 241 patients with advanced colorectal carcinoma receiving either chemotherapy alone (5-fluorouracil plus folinic acid) or the same chemotherapy plus thymostimulin [16]. Complete and partial remissions were seen in 30% of the patients in the thymostimulin arm and in 18% of controls. Chemotherapy-related toxicity to the gastrointestinal tract was significantly lower for the group receiving thymostimulin. Other treatment-related toxicity did not differ between the groups.

A rigorous RCT was published recently by Federico and associates [17]. 134 non-Hodgkin's lymphoma patients were evaluated. They received either two standardised chemotherapy regimens (MACOP-B or Pro MACE-CytaBOM) with or without thymostimulin (1 mg/kg/day on pre-set days during each course of chemotherapy). The average complete response rate in the thymostimulin groups was significantly higher than in controls (59.1 versus 42.4%). There was also a (non-significant) trend for the 4-year survival rates in the same direction (64.5 versus 43.0%). No such differences were noted for drug-related toxicity or infections. The authors stress the fact that testing the antineoplastic efficacy of thymostimulin was not the primary goal of their study. Results have, therefore, to be interpreted with caution.

COMMENT

The methodological quality of most of these RCTs is disappointing. Only one trial [9] was conducted double-blind. Multiple testing for significance without correction for it, post-hoc analyses, small sample size, insufficient description of therapeutic intervention and heterogeneous study groups are other prevalent drawbacks that seriously limit conclusions. Of these flaws, the small sample sizes are a particular worry. Due to a type II error, the majority of the studies would have overlooked even a sizeable benefit if it existed. In trials where a significant difference was detected with a low statistical power, the magnitude of the effect might be exaggerated. A small sample size would also increase the risk of uneven distribution of confounding variables.

Not all the trials evaluate the potential clinical benefit of thymus therapy for cancer. The clinical results emerging from these publications are contradictory. The majority of such trials [5, 7, 13, 16, 17] support the notion that thymus therapy is in one way or another beneficial. However, the abundance of methodological flaws mentioned above have to be taken into account. Furthermore, at least one study [17] suggests poorer survival rates in the experimental group. Adverse reactions of thymus therapy have been described repeatedly [e.g. 18, 19] and therefore deserve consideration. At least one *in vitro* study raises the possi-

Table 2. Details of preparations

Name (manufacturer)	Description	Recommended dose
Neythymun® K (vit Organ)	Bovine dried thymus extract with solvent, for injection i.c., i.m. or i.v. organ lysates standardised to three different strengths 2×10^{-6} g, 2×10^{-9} g and 2×10^{-12} g, molecular weight $<10^9$	Increasing strength 1–3 (no further details)
Thymosin α1 (biosyn)	Standardised bovine thymus extract for oral administration	3–5 times. 1–3 Drg daily.
Thymostimulin (Serono)	Bovine dried thymus extract with solvent for i.m. injection, three strengths: 10 mg, 25 mg and 50 mg	First week 0.5–1.5 mg/kg daily. Thereafter, 2–3/week.

bility that thymus extracts enhance virus DNA synthesis which could represent an undesired effect and enhance tumour growth [20].

Pre-clinical studies have demonstrated that thymus extracts restore lymphocyte function and improve immunological variables [e.g. 21, 22]. *In vitro* experiments have shown an activation of natural killer cells [e.g. 23] as well as an increase in cytotoxic activity [24]. Thymopentin also increases mitogen induced interferon levels in human lymphocytes [25–27]. Moreover, animal experiments have suggested that thymus extracts inhibit tumour growth in rats [28] and mice [29]. Therefore, a rationale for thymosin cancer therapy in humans could be developed. However, currently, the mechanism of action remains speculative [17] and our knowledge regarding the pharmacology of the various compounds used is incomplete. Table 2 summarises the published details on commercially available preparations.

In conclusion, no compelling evidence exists for the clinical efficacy of thymus therapy in human cancers. Some promising results deserve further, more rigorous investigation. Currently, thymus therapy cannot be recommended outside RCTs and should be regarded as an experimental form of therapy.

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