

Comprehensive compilation of clinical studies with thymic peptides in oncology

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Preclinical and clinical investigations with thymic peptides demonstrated recovery from primary and secondary immunodeficiencies. Epidemiological studies show an increased cancer incidence of human primary or secondary immunodeficiencies. The recovery of lymphocyte counts and especially T-cell counts and activity after myelosuppressive radiotherapy or cytostatic chemotherapy is a prognostic factor for relapse and total survival of at least some tumors like lung cancer, renal cancer, malignant melanoma, breast cancer, and lymphoma. Therefore it is expected that immunostimulation may reduce infection rate, improve quality of life and even prolong survival time.

More than 40 thymic peptides with hormonal-like activity have been defined. The biological and chemical properties of these peptides range from enhancement of T-cell proliferation, maturation and activation, induction of cytokines and apoptoses as well as augmentation of expression of cytokine receptors, to endocrine activation and direct protection against tumor growth (in mice).

Clinical studies with thymus peptides have been conducted in oncology in a variety of tumors, like breast cancer, lung cancer, gastrointestinal cancer, malignant melanoma, Hodgkin lymphoma and Non-Hodgkin lymphoma. More than 21 controlled clinical studies (phase II-III) with thymic peptides with about 1600 cancer patients involved have been published. Table I shows study design, statistical methods and clinical outcome of 22 clinical phase II and III studies published since 1979 with more than 1600 cancer patients involved. Sixteen out of these studies are prospectively randomized, partially placebo-controlled studies.

All studies confirmed protection against myelosuppression caused by immunosuppressive treatments like radio- or chemotherapy, enhanced neutrophil recovery, with consequently improved clinical conditions, like less neutropenic fever, lower incidence, duration and severity of opportunistic infections. Prophylaxis against metastases and improvement in quality of life under chemo- or radiotherapy have been reported in most of these clinical studies. In eight of these controlled studies the overall median survival time has been improved.

Antiviral effects as shown for hepatitis A, B, C and herpes simplex infections are further attributes of thymus peptides with clinical relevance.

There is some evidence that treatment of cancer patients with thymic peptides may be of appreciable benefit, especially in combination with chemo- or

Table I. Clinical phase II and III studies with thymic peptides in oncology, sum of patients 1653, number of studies 22.

Indications	Therapy	Patients (n)	Study design	Results due to thymus peptides	Remarks	References
Small-cell lung cancer (SCLC)	1. thymosin F5 20 mg/m ² s.c. 2. thymosin F5 60 mg/m ² s.c. 3. placebo s.c. (2x/wk, 6 wks)	55	randomized- placebo-con- trolled, 3 groups	median survival rate ↑ (33% vs. 9% b/w, 12% after 1 year, p < 0.05)	in combination with chemotherapy; results dose-dependent	Cohen et al. 1979 (1) see also Chretien 1997 this volume (2)
Malignant melanoma, stage III B	DTIC + BCG vs DTIC + BCG + TF 5	28	controlled study	dose-dependent results, efficacy dependent on immunocompetence	HD TF 5 (40 mg/m ²) may have beneficial effects in immuno-incompetent patients and detrimental in immunocompetent	Patt et al. 1979 (3)
Malignant melanoma; stage I, II (MM)	1. no adjuvant therapy 2. DTIC 3. thymostimulin	32	open trial with 3 groups	group 1: 13/16 metastasis; group 2: 7/8 metastasis; group 3: 2/8 metastasis; T-rosettes; IgM- and IgD- receptors: ↑	relapse rate ↓; activation of CD2+ cells and antibodies	Bernengo et al. 1983 (4)
Malignant melanoma (MM)	thymostimulin; postoperative adjuvant treatment	37	randomized study	median survival rate ↑ (p < 0.01), relapse rate ↓	cutaneous MM after surgical removal	Azizi et al. 1984 (5)
Non-small cell lung cancer (NSCLC)	thymosin-α; 0.9 mg/m ² s.c. daily for 12 months	42	randomized, placebo-con- trolled, double- blind	median survival rate ↑ (p = 0.002), relapse rate ↓; T-cell function ↑	after radiotherapy	Schuloff et al. 1985 (6)
Small-cell lung cancer (SCLC)	thymus F5 combined with cytostatics and radiotherapy 60 mg/m ² , s.c., 2x/wk	91	randomized clinical trial	response rate, response duration, median survival = ; toxicity =	limited disease (35 pts.) and extensive disease (56 pts.)	Scher et al. 1988 (7)

Table I. Continued

Indications	Therapy	Patients (n)	Study design	Results due to thymus peptides	Remarks	References
Breast cancer	thymosimulin +/- CHT	51	randomized clinical trial	TTG-group 37% and control group 77% infections	infection rate and myelotoxicity during adjuvant CHT ↓	Iaffaioli et al. 1988 (8)
Malignant melanoma (MM) stage I, II	thymosimulin vs. no treatment	55	randomized study, 2 groups stage I, II	disease free interval sign. prolonged (p = 0.02)	TS effective in high risk stage I (> 2.3 mm), not in stage II disease	Shoham 1988 (9)
Small-cell lung cancer (SCLC)	thymosimulin (1 mg/kg i.m., days 7-14 of every cycle)	26	randomized study	myelosuppression, fever and infectious episodes ↓; CR rate and survival (p > 0.0032) ↑	effects of thymostimulin on CHT-induced toxicity (myelosuppression, fever, infection)	Macchiarini et al. 1989 (10)
Non-small cell lung cancer (NSCLC)	thymosin-α ₁ (900 µg/m ² , twice weekly) + radiation therapy	87	multicenter, randomized, placebo-controlled, double-blind (RTOG)	median survival rate ↑ (p = 0.002); relapse rate ↓	patients without distant metastases; patients with progression > 3.9 months after radiotherapy	Chretien 1990 (11)
Breast cancer (b/w ovarian cancer (o))	CHT ± thymopentin (Timunox)	78 b; 37 o	controlled clinical trial with 2 groups	lymphocyte migration inhibition ↑; interferon-α i. S. ↑; survival time ↑ only in adj. chemo-immunotherapy	reduction of immunosuppressive side effects; no effects in patients with disseminated disease	Mallmann & Krebs 1990 (12)
Gastrointestinal cancer (6 met. esophageal, 16 colorectal)	low dose cyclophosphamide + thymosimulin + echinacin	22	experimental therapy	median survival time: esophageal ca. (3.5 mo.); colorectal ca. (4 mo.); activity of NK and LAK cells ↑↑	treatment of progressive disease	Lersch et al. 1992 (13)

Table 1. Continued

Indications	Therapy	Patients (n)	Study design	Results due to thymus peptides	Remarks	References
Breast cancer	CMF vs. CMF + 1.5 mg/kg thymostimulin vs. CMF + 1 mg/kg thymostimulin	68	controlled study with 3 groups	Con A+IL-2 stimulation ↑ (p < 0.005), cytotoxic activity of MØ + NK ↑ (p < 0.002), IL-2 receptors ↑ (p < 0.001) hemotoxicity ↓; response rate =; chemotherapy compliance ↑	immunomodulating effect on immunocompetent cells	Surico & Tavassoli 1992 (14)
Breast cancer	thymostimulin (1 mg/kg KG, 3 x wkl., several mo.) in combination with cytostatics (FEC)	296	randomized study with 4 groups: 1. FEC; 2. FEC + TS; 3. HDFA-FEC; 4. HDFA-FEC + TS;	metastatic breast cancer: 1668 cycles of CHT; quality of life improved by TS	Pavesi et al. 1993 (15)	
Colorectal cancer	thymostimulin (1 mg/kg, daily, i.m., several mo.) in combination with 5-FU and folinic acid	211	multicenter, randomized, controlled trial	PR+ CR sign.↑ (p = 0.02); incidence of mucositis and diarrhoea ↓ (p = 0.03)	metastatic cancer disease	Mustacchi et al. 1994 (16)
Non-small cell lung cancer (NSCLC) Malignant melanoma, metastatic	thymostimulin + CHT + radiotherapy CHT: DTIC (850 mg/m ²); IT: Tα1 (2mg) d 4-7 + IL-2 (18MU/m ² /d) d 8-12, q 3 wk	69	randomized placebo-controlled trial: single arm study	fungine infection rate ↓; NK cell activity ↑	locally advanced cancer: tolerance of antitumor treatment improved in comparison to chemotherapy alone, Tα1 modulates action of IL-2	Iuffaioli et al. 1994 (17)
Non-small cell lung cancer (NSCLC), advanced stage	thymosin-α1 1 mg days 8-11 and 15-18) + IFNα (3MU) days 11 and 18 after ifosfamide (3g/m ²) day 1, 2; q 3 wk; x6	22	randomized phase II controlled trial: CHT	36% overall response (2 complete responses); median survival time 11 months	Lopez et al. 1994 (18)	
				response rate ↑ (33% vs. 10%); time to progression ↑ (p = 0.0059); no depression of CD4+, CD8+ and NK cell counts in Tα1 group	Salvati et al. 1995 (19)	

Table 1. Continued

Indications	Therapy	Patients (n)	Study design	Results due to thymus peptides	Remarks	References
Non-Hodgkin's lymphoma (NHL) lymphoma (NHL)	thymostimulin (i.m. 1 mg/kg daily) + CHT	150	randomized multicenter trial	CR ↑ (p = 0.05); 4-year- survival rate 64.5% vs. 43% (only CHT); NK ↑, cytokines ↑	IG-NHL or HG-NHL; advantage for patients with IG-NHL and good performance status	Federico et al. 1995 (20)
Breast cancer	thymostimulin + CHT	40	randomized study	infection rate ↓ (p > 0.05); average administered dose ↑ (p > 0.05); pain sign. ↓; hydroxyproline ↓	metastatic cancer (osteolytic); first-line CHT failed	Gonnelli et al. 1995 (21)
Non-small cell lung cancer (NSCLC)	cisplatin + etoposide + IFNα2a + thymosin- α1	56	phase-II study, not randomized	median survival 12.6 months vs. 5.3–7.0 mo. in CHT- groups	43% benefited of long- lasting stable disease	Garraci et al. 1995 (22)
Breast cancer	mitoxantrone + G-CSF vs. mitoxan- trone + G-CSF + TS (50 mg/day)	54	randomized study	neutrophil recovery sign.↑ (p < 0.005), neutropenic fever in TS- group sign.↓, incidence, duration and severity of bacteriological op- portunistic infections ↓ (p < 0.002)	TS enhances hematologi- cal recovery following myelosuppressive CHT	Sánchez et al. 1996 (23)
Sum of patients		1653			No. of studies 22	

Abbreviations: adj. = adjuvant; CSF = colony stimulating factor; DTIC = dacarbazine; Tp-1 = Thymostimulin; LAK = Lymphokine Activated Killer Cells; NK = Natural Killer Cells; CR = Complete Remission; CHT = chemotherapy; NHL = Non Hodgkin-Lymphoma; TS = Thymostimulin; FEC = 5-fluorouracil, epirubicin, cyclophosphamide; RTOG = Radiation Therapy Oncology Group; Tα1 = Thymusin α1; MOX = mitoxantrone, IG-NHL = intermediate NHL; HG-NHL = high grade NHL; ↑ increase; ↓ decrease; := no change

radiotherapy, with respect to the improvement of the immunological status, reducing side effects of toxic treatments and increased remission rates and even overall survival.

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