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Effect of pentoxifylline on colon cancer patients treated with chemotherapy (Part I)

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Abstract.
BACKGROUND: Cancer progression is associated with significant systemic clinical manifestations including cachexia induced weight loss and anorexia. Pentoxifylline (PTX) is a drug that has been shown to have multiple beneficial effects in cancer patients through its anti-inflammatory properties.
MAIN OBJECTIVE: To evaluate PTX effects on colon cancer patients treated with chemotherapy.
PATIENTS and METHODS: Forty metastatic colon cancer patients receiving chemotherapy were enrolled in this randomized study. 17 patients were treated with a full dose of PTX (400 mg TID), 9 patients with a reduced dose PTX (200 mg TID) and 23 served as controls (no PTX).
RESULTS: Follow-up evaluations of patients included the following: physical examination; leukopenia determination; weight determination; stomatitis determination; and survival rate. Patients treated with PTX (both full and reduced doses), experienced a significant increase in weight and a reduction in stomatitis relative to the control group. Treatment with PTX also significantly increased patient survival rate. All patients treated with PTX, had a median overall survival (OS) rate of 20.4 months as compared to 13.2 months in the control group.
CONCLUSIONS: PTX treatment of colon cancer patients, in addition to chemotherapy, significantly improved survival rates, induced weight gain and reduced stomatitis occurrence – all important parameters of cachexia.

Keywords: Pentoxifylline, colon cancer, cachexia, weight gain, stomatitis, survival

1. Introduction

Cancer progression is associated with significant systemic clinical manifestations including cachexia-induced weight loss and anorexia. Cachexia is a complex metabolic syndrome associated with multiple chronic or end-stage diseases and is characterized by loss of muscle mass with or without an accompanying loss of fat mass. While various treatment options are recommended for cancer-related cachexia, a number have proven to be ineffective, including cyproheptadine, hydrazine and metoclopramide, with progestogens being the only treatment currently approved in Europe [1].

Pentoxifylline (PTX), a xanthine derivative, has been shown to have a marked effect on cellular mediators of inflammation and tissue injury. Cancer cachexia has been linked to elevated levels of

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inflammatory cytokines, including Tumor Necrosis Factor-alpha (TNFα), IL-6 and IL-8. PTX has been shown to inhibit TNFα production, possibly via inhibition of TNFα and IL-1 mRNA transcription with relative preservation or even an increase of IL-10, an anti-inflammatory cytokine [2, 3]. In a separate study, PTX was shown to decrease TLR-mediated TNFα mRNA while increasing IL-10 mRNA [4, 5].

It has also been suggested that PTX reduces chemotherapy-induced stomatitis through the effect of these same inflammatory cytokines. In one study, a combination of PTX and vitamin E was assessed for the treatment of radiotherapy-induced oral mucositis. The combination decreased the duration of oral mucositis and dysphagia, and the occurrence of dysgeusia and fatigue without compromising locoregional control. This study concluded that the combination of PTX and vitamin E reduced the severity and duration of acute radiotherapy-induced oral mucositis and dysphagia in HNC patients [6, 7].

PTX not only possesses anticancer activity itself but increases cancer cell susceptibility to radiation therapy while reducing resultant long-term side effects [1, 2]. Recently suggested treatments for cancer-related cachexia have involved different therapeutic combinations including PTX, anti-TNFα monoclonal antibodies (MoAb) and selective COX-2 inhibitors. Neonatal plasma factors were shown to contribute to the anti-inflammatory effects of PTX in new-born blood that were independent of soluble TNFα Receptor levels, p38 MAPK phosphorylation and IκB degradation [2, 8].

One of the latest approaches in anti-cancer therapeutics includes utilizing PTX in combined anti-cancer therapies [9–12]. A double blind, randomized, placebo-controlled clinical trial, demonstrated that PTX did not have any significant effect on weight gain in cachectic patients, but improved short-term quality of life [11]. This is an exception, as majority of papers on the subject show positive results of PTX on weight gain and stomatitis.

The main aim of this study is to evaluate the effects of PTX on cachexia-related end points, including weight gain, stomatitis occurrence, blood counts, and on overall survival rate.

2. Patients and methods

Forty patients diagnosed with metastatic colon cancer were enrolled in this randomized study.

All patients were receiving chemotherapy, a combination of 5-fluorouracil (5-FU) and leucovorin, administered for 5 consecutive days, every 3 weeks until progression of disease or death.

Patients were randomized to either the treatment arm, receiving PTX or the control arm- no PTX.

A total of 17 patients were placed into the treatment arm, where 8 patients received a full PTX dose (400 mg, TID) and 9 patients received a reduced PTX dose (200 mg, TID). These 9 patients did not tolerate the PTX treatment well due to side effects (including nausea, headache or dizziness) and as a result received treatment for a few weeks only. A total of 23 patients were randomized as controls and did not receive any PTX.

The study was reviewed, conducted and approved by the Hadassah - Hebrew University Medical Center Helsinki Committee (0346-12-HMO, 1.1.17).

All patients were assessed every 3 weeks (First 3 weeks – Time point 1, 6 weeks – Time point 2, 9 weeks – Time point 3 based on the following criteria and measurements:

* Physical examination
* Whole blood counts
* Weight measurement
* Stomatitis development
* Overall survival (OS calculated from initiation of chemotherapy with PTX).

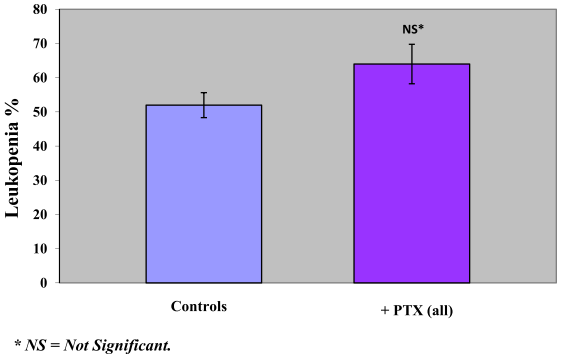

Fig. 1. Leukopenia of PTX-treated and control patients.

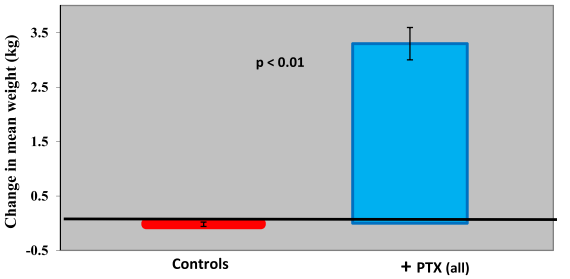

Fig. 2. Change in mean weight of groups in PTX-treated and control patients.

2.1. *Statistical analysis*

All statistical tests were performed using the SPSS statistical package.

3. Results

The results of the study include the following end point measurements:

- Whole blood counts – Leukopenia
  No statistically significant difference was found between the PTX-treated patients and the control group (see Fig. 1). 5-FU is notorious for affecting bone marrow and platelet blood counts (all lines), however compared to other chemotherapies the effect is relatively modest. Since PTX has no major bone marrow effects bone marrow was not affected in the patients of this study.
- Weight – patients treated with PTX (both the full and reduced doses), gained a significant amount of weight during the treatment period as compared to the controls. The mean increase in weight of PTX-treated patients was 3.3 kg, where a significant mean weight reduction of 0.2 kg in the control group was seen (Fig. 2) ($p < 0.01$).
- Stomatitis – the presence of stomatitis was assessed in patients treated with PTX (both full and reduced doses) and in the controls group. A gradual decrease in stomatitis cases was observed when comparing controls vs PTX full dose or PTX reduced dose: 45.5% of the control patients

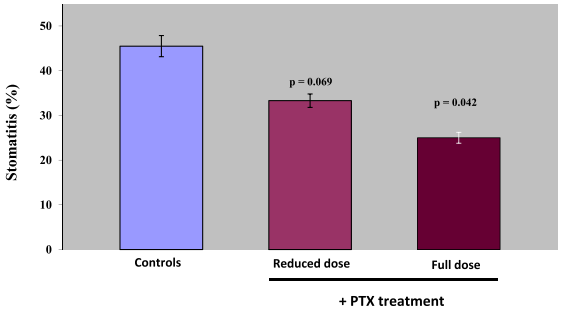

Fig. 3. Stomatitis (%) in PTX-treated and control patients.

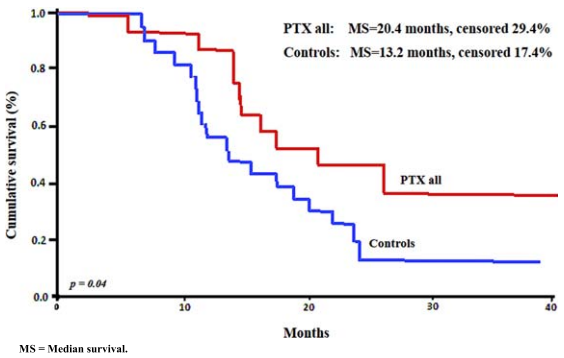

Fig. 4a. Cumulative survival of PTX-treated patients and controls.

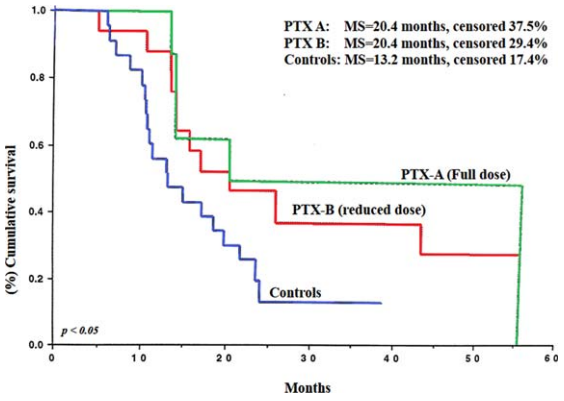

Fig. 4b. Cumulative survival of PTX-treated and control patients.

developed stomatitis, 33.3% of PTX reduced dose patients developed stomatitis, while only 25% of full dose PTX patients developed stomatitis (Fig. 3) ($p < 0.05$).

- Survival – treatment with PTX had a beneficial effect on survival. Patients treated with the *full dose of* PTX (400 mg, TID) had a median survival time of 20.4 months and 37.5% of them censored.

Patients treated with the *reduced PTX dose* (PTX 200 mg, TID) also had a median survival time of 20.4 months, but 29.4% of them censored. The control group had a median survival time of 13.2

months and only 17.4% of patients censored ($p < 0.05$) (Fig. 4a). Survival follow up of patients was performed up to 5 years post-study initiation, providing significant insight into long-term effects (Fig. 4b).

The initiation of the increasing effects of PTX on survival can clearly be seen from the Kaplan Meyer graphs 8 months post-study initiation (Fig. 4a).

Patient demographics and specifics are summarized in the following Tables 1–4:

Table 1
Characteristics of PTX-treated cancer patients and controls

Patient No.	Age (y)	Sex	Height (cm)	Sites
PTX treated				
11	61	M	175	Recto-sigmoid
12	72	M	174	Colon
14	63	F	177	Recto-sigmoid
2	53	F	184	Colon
28	58	M	180	Colon
6	48	M	169	Colon
7	48	M	163	Recto-sigmoid
8	69	M	155	Recto-sigmoid
15	58	M	166	Colon
17	67	M	153	Recto-sigmoid
19	72	F	175	Colon
20	70	M	168	Colon
24	68	F	162	Colon
27	52	F	162	Colon
3	71	M	157	Recto-sigmoid
4	75	F	178	Recto-sigmoid
9	64	F	150	Colon
Controls				
1	22	M	174	Recto-sigmoid
10	64	F	165	Colon
13	42	M	160	Recto-sigmoid
16	41	F	160	Recto-sigmoid
18	76	M	161	Recto-sigmoid
21	67	F	161	Recto-sigmoid
22	70	M	165	Colon
23	68	F	163	Colon
25	41	F	179	Colon
26	50	M	158	Recto-sigmoid
29	65	F	145	Colon
30	72	F	165	Recto-sigmoid
31	59	M	173	Recto-sigmoid
32	64	M	166	Recto-sigmoid
33	71	M	169	Colon
34	49	M	178	Colon
35	42	M	176	Recto-sigmoid
36	69	F	161	Recto-sigmoid
37	55	M	173	Colon
38	54	M	174	Colon
39	68	F	145	Recto-sigmoid
40	59	F	156	Recto-sigmoid
5	65	M	160	Colon

Table 2
Colon Cancer patients - Concomitant diseases and medications

Patient No.	Diseases*	Treatments**
Controls		
1	1,3	Convertin, Diabinese
10	4	Tegretol, Idantoin, Mysoline
13	5	–
16	5	–
18	1	Daonil
21	2,4	Normiten, Cardoxin, Thiazide
22	1,4	Normiten, Pressolat
23	4	Nopan, Clonex
25	4	–
26	4	–
29	3,4	Daonil, Cimetidine, Zantac
30	4	Eltroxin, Idantoin, Dexamethasone, Zantac
31	4	Pancreatin, Metamucil
32	5	–
33	1,2,3,4	Normiten, Glucophage, Daonil.
34	5	–
35	5	–
36	5	–
37	4	Tagamet
38	1,3	Normiten, Glibetic
39	2	Aspirin
40	4	Digoxin, Aspirin
5	5	–
PTX treated		
11	1,2,4	Nitroglycerin, Percocet
12	5	–
14	5	–
2	1,2,4	Digoxin, Fusid, SlowK, Ikacor, Losec, Clexane, Cordil; Tiloptic, Pilocarpine, Normiten, Pressolat, Zylol
28	4	Clexane
6	4	–
7	5	–
8	5	–
15	4	Tagamet, +MMC, Zn
17	4	Sucralfate, Zantac, Percocet
19	5	HRT
20	2,4	Adalat, Cordil, Lovalip, Convertin, Aspirin, Percocet
24	5	
27	1,2,4	Lopressor, Atarax
3	1,2,4	Ikacor, Cordil, Cardoxin, Zantac, Normiten.
4	4	Ferrocal
9	1,3,4	Convertin, Normiten, Dilatin

Diseases*: 1- Diabetes Mellitus, 2- IHD, 3-Hypertension, 4-other, 5-None.

Table 3
Comparison between PTX-treated and control patients

	PTX-treated	Controls	Significance
Sex - M/F	10/7	13/10	NS
Age - mean (y)	62.9	58.8	NS
Height - females (cm)	159	160	NS
Height - males (cm)	168.2	171.8	NS
Height - all (cm)	166.9	164.2	NS
Diagnosis:			
Colon cancer	10	10	NS
Recto-sigmoid	7	13	NS
Stage	Metastatic	Metastatic	NS

Table 4
Side effects of all study patients

	PTX treated ($n = 17$)	Controls ($n = 23$)
Leukopenia	11	12
Thrombocytopenia	7	9
Vomiting	6	4
Nausea	8	6
Diarrhea	7	7
Stomatitis	5	10
Alopecia	1	1

4. Discussion

This study showed that both reduced and full dose PTX in metastatic colon cancer patients receiving a combination of 5-FU and leucovorin had beneficial effects in terms of survival, cachexia and select side effects of chemotherapy (stomatitis and weight loss). These effects were demonstrated for all patients receiving PTX, both in full and reduced treatment doses.

PTX has been shown as a potent and efficacious inhibitor of TLR-mediated inflammatory cytokines in new-born cord blood and a promising neonatal anti-inflammatory agent [2]. All patients treated with PTX had a median OS of 20.4 months as compared to only 13.2 months in the control group. Moreover, 37.5% of patients receiving the full dose of PTX and 29.4% receiving the reduced dose were alive about 5 years post-initiation of the study as compared to 17.4% in the control group. This significant result incurs interest and shows potential for future studies assessing the effects of low dose PTX treatment in cancer patients. In addition, PTX may be assessed with different combinations and regimens of multi-drug chemotherapies. Even if life expectancies do not change significantly with these approaches, quality of life of patients may be improved.

In PTX-treated patients, a significant weight gain was observed (mean 3.2 kg) as compared to the control group, wherein an opposing effect, weight reduction occurred (mean 0.2 kg). Weight is not only considered the optimal clinical parameter for cancer-related cachexia progression but is also strongly associated with overall patient well-being [11, 13, 14].

Stomatitis is a major side effect of 5-FU based chemotherapy, causing significant morbidity. Patients treated with PTX developed stomatitis to a lesser degree than those in the control group. This fact

together with the weight gain observed in the PTX-treated patients is an evidence of improved quality of life in such patients.

Results of one study showed that PTX in the treatment of cancer cachexia did not have any effect on weight gain in cachectic patients, however with short-term (1 month) treatment the quality of life was improved [11]. In other studies, PTX reduced the side effects of various treatments [12, 13].

The results of this study were comparable to those of other controlled clinical studies [6, 7, 11, 13, 14]. While our study included only 40 patients, the other studies were performed on 70 patients [11], 59 patients [6] and 60 patients [7]. In our study part II [15], we will show the beneficial effects of PTX caused by decreasing levels of inflammatory cytokines *vs* their increases in the controls.

In acute inflammatory diseases such as sepsis or current pandemics, such as COVID-19, patients are displaying a severe inflammatory cytokine syndrome referred to as a "cytokine storm".

Recently, it has been shown that COVID-19 causes severe lung inflammation, often leading to death. Preliminary results on using PTX in the COVID-19 pandemic for treatment of the cytokine storm, which is characteristic of patients suffering from a severe state of the disease, were published this year [16, 17].

High inflammatory cytokines, have been documented in patients with coronary artery disease [18], and PTX has been shown to reduce this pro-inflammatory process [19–21].

With regards to survival time, we evaluated patients for about 5 years post-study initiation, while other studies had a more limited follow up time of 6 months and 2 years [6, 7]. The parameters assessed in the majority of studies were blood tests, weight assessment, stomatitis and OS, as in our study.

5. Conclusion

This randomized study demonstrated that PTX diminishes cachexia-related parameters, including weight gain, stomatitis and most importantly improves overall survival, in colon cancer patients treated with chemotherapy.

PTX, which is known to reduce the production of inflammatory cytokines and tumor markers (which will be demonstrated in Part II of this study [15], shows significant potential as a beneficial drug in severe symptomatic colon cancer patients.

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Author contributions

DATA CURATION: AM and TP
ANALYSIS OF DATA: LB, SS and VB
PREPARATION OF THE MANUSCRIPT: VB
REVISION FOR IMPORTANT INTELLECTUAL CONTENT: VB

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