

Research Paper

Progression-free Survival Decreases with Each Subsequent Therapy in Patients Presenting for Phase I Clinical Trials

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Abstract

Background: There is often a finite progression-free interval of time between one systemic therapy and the next when treating patients with advanced cancer. While it appears that progression-free survival (PFS) between systemic therapies tends to get shorter for a number of factors, there has not been a formal evaluation of diverse tumor types in an advanced cancer population treated with commercially-available systemic therapies.

Methods: In an attempt to clarify the relationship between PFS between subsequent systemic therapies, we analyzed the records of 165 advanced cancer patients coming to our clinic for consideration for participation in six different phase I clinical trials requiring detailed and extensive past medical treatment history documentation.

Results: There were 77 men and 65 women meeting inclusion criteria with a median age at diagnosis of 55.3 years (range 9.4-81.6). The most common cancer types were colorectal (13.9%), other gastrointestinal (11.8%), prostate (11.8%). A median of 3 (range 1-11) systemic therapies were received prior to phase I evaluation. There was a significant decrease in PFS in systemic therapy for advanced disease from treatment 1 to treatment 2 to treatment 3 ($p = 0.002$), as well as, from treatment 1 through treatment 5 ($p < 0.001$).

Conclusions: In an advanced cancer population of diverse tumor types, we observe a statistically significant decrease in PFS with each successive standard therapy. Identification of new therapies that reverse this trend of decreasing PFS may lead to improved clinical outcomes.

Key words: Progression-free survival, chemotherapy, advanced cancer, systemic therapy, phase I clinical trials

Introduction

The treatment of advanced/metastatic cancer often involves systemic chemotherapy. The most robust responses and lengthiest interval of time before disease progression is usually observed with first-line therapy^{1,2,3}. Often, when progression occurs on first-line therapy, subsequent systemic therapies are offered in patients who are eligible for additional

therapy based on clinical attributes such as performance status and acceptable laboratory parameters. Subsequent therapies are selected based on tumor type and treatment guidelines, availability of approved agents or off-label use of approved agents, or when feasible, eligibility to participate in a clinical trial involving systemic therapy of an investigational

agent. It has been noted that the interval of time between subsequent therapies in advanced/metastatic cancer is reduced after each treatment. For example, progression-free survival (PFS) shortens such that Treatment A > Treatment B > Treatment C > Treatment D, and so on^{1,2,3}. Examination of the relationship between PFS and its impact on disease progression in advanced/metastatic cancer patients leading up to evaluation for participation in a phase I clinical trial has been limited.

Clinical factors that may affect the length of survival during phase I clinical trials for patients with advanced cancers have been identified. Patients receiving more than five prior treatments had a trend toward shorter survival⁴. A longer median PFS has been observed in lung cancer patients treated on phase I studies that had received two or less prior therapies compared to lung cancer patients treated with more than two prior therapies⁵. While it appears that PFS tends to get shorter for a number of factors (e.g. tumor progression, toxicity, or patient wishes), there has not been a formal evaluation in an advanced cancer population of diverse tumor types treated with commercially-available systemic therapies. We examined PFS between systemic therapies of commercially available agents prior to presenting for a phase I clinical trial evaluation at our institution.

Materials and Methods

Participants were all adults with a diagnosis of advanced/metastatic cancer at the time of signed informed consent for screening for a Phase I clinical trial at our center. All patients were selected for inclusion in this analysis because they consented for at least one of six of our phase I trials which require detailed past medical treatment histories, including prior treatment start and stop dates, past surgeries and radiotherapy treatment dates, as part of screening. Clinical characteristics collected include: subject diagnosis, histology, age, gender, stage at diagnosis, prior chemotherapy, prior surgery and radiation therapy, and PFS on systemic therapy for advanced/metastatic cancer was calculated from start of the first systemic therapy regimen for advanced/metastatic cancer (tx_n) to the start of the next subsequent systemic therapy (tx_{n+1}), then tx_{n+1} and tx_{n+2} , and so on. PFS between consecutive systemic therapies were calculated using the Jonckheere-Terpstra test. NOTE: if there was a palliative surgical or radiation intervention between one type of systemic therapy (e.g. tx_{n+2} and tx_{n+3}), then additional PFS calculations were resumed from the starting point tx_{n+3} to the start of tx_{n+4} , such that PFS was not calculated between start of tx_{n+2} and tx_{n+3} .

Each patient's medical history was reviewed from the time of cancer diagnosis to presentation at our institution for clinical trial evaluation to determine the PFS for each line of therapy. Surgery, radiotherapy, herbal supplements, and investigational therapies were censored. Standard therapies given to patients subsequent to investigational therapies were censored from the data set. Progression dates were defined by the start date of the next chemotherapy agent given. When the exact day of the month for start or stop of a therapy was not provided, the 15th of the month was assigned. When start and progression dates lacked information about the specific month or year, the treatment information was censored.

Results

Patient Characteristics

We reviewed the patient records of 165 unique patients that were evaluated for participation in six phase I trials. Due to a lack of specific start/stop dates, 25 patients had at least one treatment censored for analysis; with one of these patients not having PFS that could be calculated for this study. Seventeen of these twenty-five patients were diagnosed as having less than stage IV disease, with the majority of censored treatments (radiation, surgery, or neoadjuvant or adjuvant chemotherapy) occurring in the non-advanced/metastatic setting. One hundred forty-four patients met criteria for receiving at least one prior non-investigational systemic therapy for advanced/metastatic cancer prior to coming for a phase I treatment evaluation. There were 77 men and 65 women; median age at cancer diagnosis was 55.3 years (range, 9.4 - 81.6 years). The most common types were: colorectal cancer (n=20 (13.9%)), other gastrointestinal cancer (n=17 (11.8%)), adenocarcinoma of the prostate (n=17 (11.8%)), non-small cell lung cancer (NSCLC) (n=13 (9.0%)), breast cancer (n=12 (8.3%)), ovarian cancer (n=11 (7.6%)), and adenocarcinoma of the pancreas (n=9 (6.3%)) (Table I). Patients had a median of three chemotherapy or hormonal treatments (mean, 3.32 treatments; range, 1 - 11 treatments).

Two of the 144 patients did not receive a second systemic therapy prior to evaluation at our center, so PFS could be calculated for the remaining 142 patients. The PFS from tx_n to tx_{n+3} was significantly decreased ($p = 0.001850$) (Figure 1). Few advanced cancers have more than four lines of FDA-approved or consensus guidelines recommendations for systemic therapy, thus we examined the time to progression of the first five treatments ($p = 2.938e-07$) (Figure 2).

Table I. Patient Diagnoses, Gender, Median Age at Diagnosis and Median Number of Therapies

	Number of Patients*	Male	Female	Median Age at Diagnosis (range) (in years)	Median Therapies (range) (in years)
Total	142	77	65	55.7 (9.4-81.6)	3 (1-11)
Colorectal	20	11	9	55.3 (33.1-79.9)	4 (2-9)
Other Gastrointestinal	17	12	5	54.0 (9.4-72.9)	2 (1-10)
Prostate	17	17	0	60.3 (52.0-75.2)	3 (2-8)
Breast	12	1	11	44.9 (28.0-57.3)	7 (3-11)
Non-small-cell Lung	13	9	4	63.9 (41.6-81.6)	3 (1-4)
Ovarian	11	0	11	59.8 (44.2-75.3)	4 (2-9)
Pancreatic	9	6	3	61.0 (31.7-79.6)	1 (1-4)
Gynecological	8	0	8	39.6 (24.4-69.7)	1.5 (1-3)
Head and Neck	8	6	2	51.9 (45.3-72.3)	2 (1-8)
Skin	7	6	1	48.2 (32.0-73.3)	2 (1-3)
Other	6	1	5	52.4 (39.5-62.7)	2 (1-5)
Small-cell Lung	4	0	4	55.9 (50.0-66.2)	2.5 (2-3)
Genitourinary	3	3	0	53.2 (19.5-66.6)	3 (2-4)
Sarcoma	3	2	1	66.7 (29.9-78.0)	2 (1-3)
Thoracic	3	2	1	37.9 (19.6-60.1)	1 (1-4)
Adrenal	1	1	0	54.0 (54.0-54.0)	1 (1-1)

"Other" include: unknown primary (n=2), carcinoma (n=1), eccrine sweat gland (n=1), leiomyosarcoma (n=1), ocular melanoma (n=1).

*Does not include patients that were censored from analysis.

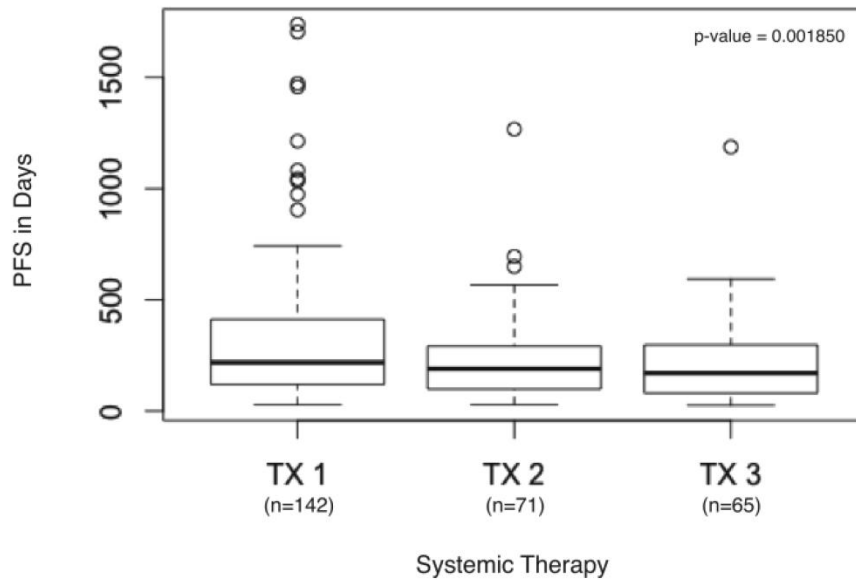


Figure I. PFS in days from first systemic therapy to third systemic therapy. Boxplot detail showing significant decrease in PFS calculated for first systemic therapy (TX1), second systemic therapy (TX2), and third systemic therapy (TX3) in days.

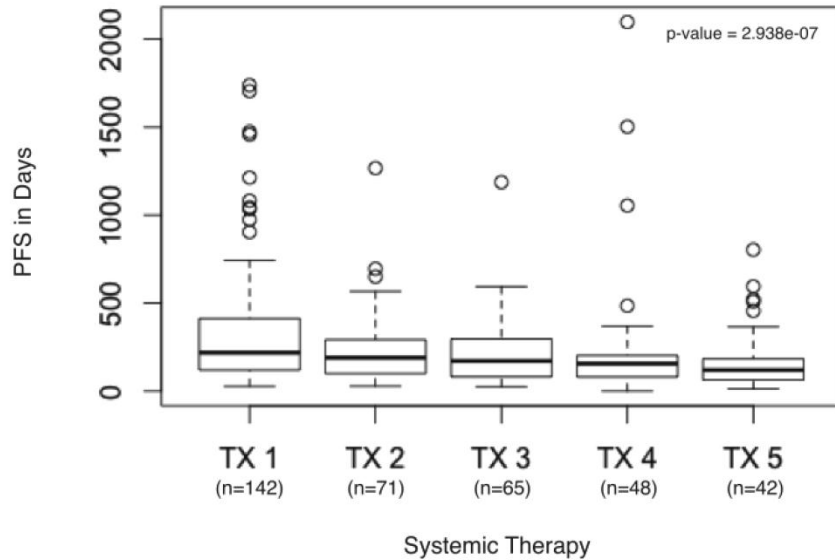


Figure 2. PFS in days from first systemic therapy to fifth systemic therapy. Boxplot detail showing significant decrease in PFS calculated for first systemic therapy (TX1), second systemic therapy (TX2), third systemic therapy (TX3), fourth systemic therapy (TX4), and fifth systemic therapy (TX5) in days.

Discussion

Statistical analyses revealed that there was a significant downward trend in PFS for patients on three standard therapies ($p = 0.001850$) (Figure 1). Most patients with advanced cancers have no more than four lines of approved treatment, we also examined the PFS of the first five treatments, again finding a significant downward trend ($p = 2.938e-07$) (Figure 2).

Other reports support these findings of decreased PFS with subsequent therapies. In colorectal cancer, the median PFS is 6-10.6 months⁶⁻¹⁵, 2.3-7.3 months¹⁶⁻²⁰, and 5.3-5.4 months^{21,22} for first-, second-, and third-line systemic therapies; respectively. In NSCLC, the median PFS is 4.2-13.1 months²³⁻³³ and 1.7-4.6 months³⁴⁻⁴³ for first- and second line-treatment; respectively. In gastro-esophageal cancer, the median PFS is 3.9-7.0 months⁴⁴⁻⁴⁹ and 1.8-4.1 months⁵⁰⁻⁵² for first- and second-line therapy; respectively. The least favorable results are in patients with advanced pancreatic cancer, where the median PFS is 3.3-6.4 months^{53,54} and 1.4-4.1 months⁵⁵⁻⁵⁹ for first- and second-line treatment; respectively (Table II).

A reversal of decreasing PFS with therapy may suggest a change in the expected course of the disease. Recent examples of new therapies that have dramatically changed the disease course for patients with advanced cancer include targeted cancer therapies such as imatinib for chronic myelogenous leukemia and gastrointestinal stromal tumors (GIST) and erlotinib for NSCLC. In GIST patients treated with

imatinib, a specific exon mutation in the tumor correlates with a higher response rate, PFS, and overall survival (OS)⁶⁰⁻⁶². In NSCLC, it is the activating tyrosine kinase mutation in the tumor’s EGFR gene that dramatically sensitizes this cancer to erlotinib and gefitinib⁶³⁻⁶⁷. These mutations had first been observed in clinical subgroups of NSCLC patients, primarily, Asian never-smoker women with adenocarcinoma^{60,68-71}. Potential “therapeutic efficacy” subgroups may be recognized when a reversal in the expected decreasing PFS during therapy is observed.

Table II. Progression-free Survival for Successive Treatments in Supporting Articles. KEY: TX 1 – PFS for first-line systemic therapy, TX 2- PFS for second-line systemic therapy, TX 3- PFS for third-line systemic therapy.

Cancer Type	TX 1 (months)	TX 2 (months)	TX 3 (months)
Colorectal	6-10.7	2.3-7.3	5.3-5.4
Non-small cell Lung	4.2-13.1	1.7-4.6	-
Gastro-esophageal	3.9-7.0	1.8-4.1	-
Pancreatic	3.3-6.4	1.4-4.1	-

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Conflict of Interest

There are no financial disclosures from any authors.

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