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TITLE
Attrition of Patients on a Precision Oncology Trial: Analysis of the I-PREDICT Experience

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Patient Attrition: I-PREDICT Experience

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KEYWORDS
precision medicine, neoplasms, genome, molecular targeted therapy, genetic profiling

ABSTRACT

Background

Precision oncology uses molecular profiling of tumors to identify biomarker-tailored therapies for patients in the hope of improving outcomes. Typically, only a minority of patients receives evaluable matched treatment. This study explored the reasons for attrition on a precision medicine trial.

Materials and Methods

Study participants were 190 adult patients consented to the I-PREDICT (Investigation of molecular Profile-Related Evidence Determining Individualized Cancer Therapy) trial. Patients had metastatic and/or unresectable incurable malignancies. Inevaluable patients were analyzed.

Results

Of consented patients, 44% were inevaluable. Men were twice as likely to be inevaluable as women. Prominently, 45% of inevaluable patients dropped off due to death, hospice referral, or decline in organ function.

Conclusion

Health deterioration of consented patients is a significant barrier to being evaluable on the I-PREDICT trial. These data suggest that patients are enrolled on precision oncology trials too late in their disease course or with excessive disease burden.

INTRODUCTION

Genome-driven cancer care is predicated on the presence of actionable alterations for which targeted therapies exist. Molecular profiling of tumors has become more common.

Studies have demonstrated that profiling identifies actionable alterations in 40% to 95% of patients [1-10]. However, only 5% to ~50% of eligible patients were treated with matched therapies [1-10].

Limited studies have explored this low rate of matching and treatment in precision oncology trials. Common barriers include the discretion of treating oncologists, access to drugs, and the timing of profiling in advanced disease [1-6]. The current study investigated patient attrition in the Investigation of molecular Profile-Related Evidence Determining Individualized Cancer Therapy (I-PREDICT) [10] trial.

MATERIALS AND METHODS

I-PREDICT Trial

The I-PREDICT trial (ClinicalTrials.gov Identifier: NCT02534675) uses genomic profiling to match patients to treatment [10]. Next-generation sequencing from Foundation Medicine profiled tumors (Cambridge, Massachusetts; http://www.foundationmedicine.com). These assays have been previously described [10]. Based on profiling results, a Molecular Tumor Board recommended therapies to treating oncologists. All patients consented to an Institutional Review Board-approved protocol.

Participants

The first 190 enrolled patients, beginning February 13, 2015, at the University of California, San Diego (UC San Diego) Moores Cancer Center site were included. Eligibility criteria for the I-PREDICT trial have been previously outlined [10]. Participants were adults (age ≥18 years) with an incurable metastatic or unresectable malignancy that was treatment

naïve and with ≥50% 2-year mortality, or previously treated that had failed standard therapies or had no standard therapy.

Data Analysis

A secondary analysis of the I-PREDICT trial data was performed. Demographic and clinicopathologic characteristics were described for inevaluable and evaluable patients. Inevaluable patients were subdivided: untreated (since consent) and treated (with ≥1 dose of anti-cancer drug after consent). (S**ee Supplemental Materials and Methods**)

RESULTS

Patient Characteristics

Of the 190 total patients, the median age was 62 years (range: 21-93 years); 59% were women ($n = 112$); 66% were Caucasian ($n = 125$). Over half had gastrointestinal cancers ($n = 103$, 54%). Most patients had received prior treatment ($n = 123$, 65%). Of these, the median number of prior lines of therapy was 2 (range: 1-11 therapies). At enrollment, 57 patients (30%) had excellent performance status. Overall, 56 patients (29%) died within 6 months, and 33 (17%) within 3 months of consent. In this cohort, 4% were awaiting treatment ($n = 8$), 52% were evaluable ($n = 99$), and 44% were inevaluable ($n = 83$). Of the 83 inevaluable patients, 28% were inevaluable treated ($n = 23$) and 72% were inevaluable untreated ($n = 60$) (**Table 1**, **Figure 1**).

Characteristics Associated with Being Inevaluable

Of the 83 inevaluable patients, more men (54%) than women (37%) were inevaluable ($P = .04$). Gastrointestinal cancer patients tended to be inevaluable ($P = .16$). However, only gender was independently associated with inevaluable status; men were twice as likely to be inevaluable

as women (odds ratio = 2.0, 95% confidence interval: 1.1-3.9, $P = .03$, multivariable analysis) (**Table 1**).

Reasons for Being Inevaluable

The most common reason for being inevaluable was the deteriorating health of patients, which led to early discontinuation of treatment, hospice care, or death ($n = 31$, 37% of 83 inevaluable patients), plus another 7% who had inadequate organ function ($n = 6$ of 83 patients). Hence, health decline explained 45% of inevaluable patients ($n = 37$ of 83 patients). Treatment delays, usually for personal reasons, accounted for 14% of patients ($n = 12$ of 83 patients). Only 12% experienced molecular profiling issues ($n = 10$ of 83 patients), and 8% were lost to follow-up ($n = 7$ of 83 patents). Notably, only 1 patient had insufficient insurance coverage (1.2% of 83 patients) (**Figure 1**).

DISCUSSION

Matched molecularly targeted therapies may yield improved cancer outcomes [2, 4-7]. Nevertheless, most patients in precision medicine trials remain untreated/unmatched [1-10]. We explored patient attrition in the I-PREDICT trial, which uses genomic sequencing to navigate patients to therapy [10]. Of 190 consecutively enrolled patients, 44% were inevaluable ($n = 83$). Only male gender was independently associated with inevaluable status ($P = .03$, multivariable analysis). Prominently, 45% of attrition ($n = 37$ of the 83 inevaluable patients; 19% of 190 consented patients) was attributable to declining health. Other studies also reported that patients were frequently inevaluable on precision medicine trials because of death or hospice transfer [2, 4, 8-9].

Studies have also reported that patient access to matched clinical trials/therapies was hindered by extensive inclusion criteria, insurance denial, travel restrictions, and lack of available protocols [2, 5-7]. In contrast, only one I-PREDICT patient dropped off due to lack of insurance coverage, and drug access was not a significant barrier in the I-PREDICT trial. Clinical trial navigators and medication acquisition specialists, who are devoted to ensuring that patients receive treatment, and a just-in-time Molecular Tumor Board, are incorporated into the workflow of the trial to circumvent these barriers.

The treatment rate in the I-PREDICT cohort was high for a precision medicine trial (52%). This may be partly explained by the few molecular profiling issues experienced in the I-PREDICT trial (5%, $n = 10$ of 190 consented patients). In addition to the design features of the trial discussed above, identifying actionable alterations in I-PREDICT patients may have been facilitated by using a large gene panel as well as blood-based sequencing. Studies have shown that such assays can identify actionable alterations in up to 90% of patients [2, 4], suggesting that the treatment rate can still be improved.

CONCLUSION

Health deterioration of patients after consent is a significant barrier to being evaluable on the current genome-driven precision oncology trial (I-PREDICT) [10]. Studies should investigate tumor burden, pace of progression, and other features that might correlate with imminent worsening. Consideration should be given to ensuring that patients are enrolled on precision medicine studies before their condition is in rapid decline.

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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Table 1. The I-PREDICT Trial: Characteristics of Consented Patients (University of California San Diego site)

Parameter[a]	**Evaluable**	**Inevaluable**	**Group Difference**[g] [*P* value]	**Univariable (inevaluable vs evaluable)**[g,h] [OR, 95% CI, *P* value]	**Multivariable (inevaluable vs evaluable)**[g,h] [OR, 95% CI, *P* value]	**Awaiting Treatment**[i]
Consented[b], *N* = 190	99 (52%)	83 (44%)				8 (4%)
Age [years]			.51			
median = 62 (range: 21-93)	62 (21- 93)	63 (27 – 93)				59 (41-82)
<62, *n* = 94 (49%)	50 (53%)	39 (42%)		reference		5 (5%)
≥62, *n* = 96 (51%)	49 (51%)	44 (46%)		1.2, 0.6-2.1, .64		3 (3%)
Gender			**.04**			
Female, *n* = 112 (59%)	64 (57%)	41 (37%)		reference	reference	7 (6%)
Male, *n* = 78 (41%)	35 (45%)	42 (54%)		1.9, 1.0-3.4, **.04**	2.0, 1.1-3.9, **.03**	1 (1%)
Ethnicity/Race			.34			
Caucasian, *n* = 125 (66%)	68 (54%)	50 (40%)		0.8, 0.4-1.6, .56		7 (6%)
Hispanic, *n* = 22 (11%)	9 (41%)	13 (59%)		1.6, 0.6-4.6, .38		0
Other[c], *n* = 43 (23%)	22 (51%)	20 (47%)		reference		1 (2%)
Tumor type[d]			.36			
Gastrointestinal, *n* = 103 (54%)	50 (49%)	49 (47%)		1.6, 0.8-3.1, **.16**	1.5, 0.8-2.9, .24	4 (4%)
Gynecological, *n* = 27 (14%)	13 (48%)	12 (45%)		1.5, 0.6-3.9, .39		2 (7%)
Other, *n* = 60 (32%)	36 (60%)	22 (37%)		reference	reference	2 (3%)

Treatment status before trial			.31		
Prior treatment, *n* = 123 (65%)	68 (55%)	51 (42%)		reference	4 (3%)
Treatment naïve, *n* = 67 (35%)	31 (46%)	32 (48%)		1.4, 0.7-2.5, .31	4 (6%)
Prior therapies[e]			.94		
median = 2 (range: 1-11)	2 (1-11)	2 (1-7)			1 (1-4)
<2, *n* = 94 (49%)	28 (58%)	18 (38%)		reference	2 (4%)
≥2, *n* = 96 (51%)	40 (53%)	33 (44%)		1.3, 0.6-2.7, .52	2 (3%)
ECOG status[f]			.24		
0, *n* = 57 (30%)	33 (58%)	21 (37%)		reference	3 (5%)
≥1, *n* = 133 (70%)	66 (50%)	62 (46%)		1.5, 0.7-2.9, .24	5 (4%)
Death after consent					
<3 months, *n* = 33 (17%)	16 (48%)	17 (52%)	.45		0
<6 months, *n* = 56 (29%)	28 (50%)	28 (50%)	.43		0

Notes: Data are presented as *n* (%), unless otherwise stated.

Abbreviations: OR = Odds ratio; CI = confidence interval; ECOG = Eastern Cooperative Oncology Group

[a]All parameters were from the time of consent.

[b]Only patients consented at the University of California, San Diego site. There was a total of 190 patients. These included 182 evaluable and inevaluable patients and 8 awaiting treatment.

[c]Includes non-Hispanic ethnicity of Asian, Black or African American, other, and declined to state races.

[d]Gastrointestinal tumor type includes 28 hepatobiliary and pancreatic cancers. Other tumor types are all tumor types other than gastrointestinal and gynecological. A detailed profile of tumor types is in **Supplemental Table 1**.

[e]Number of prior systemic therapies, including adjuvant or neoadjuvant, only amongst patients receiving prior treatment before enrollment in the I-PREDICT trial (n = 123, 65%).

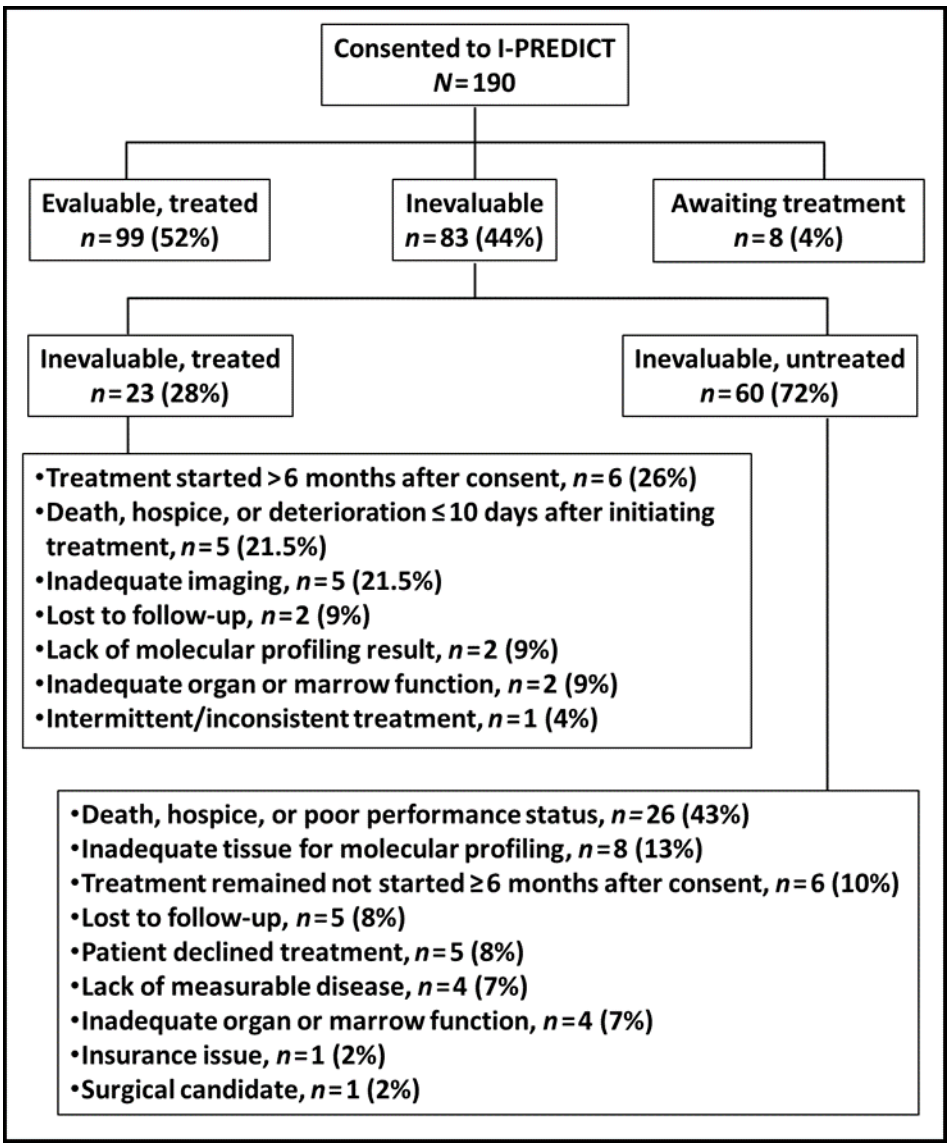
[f]Eastern Cooperative Oncology Group (ECOG) Performance Status.

[g]Comparison between evaluable and inevaluable patients, excludes 8 patients awaiting treatment for less than 6 months.

[h]Association between inevaluable status and parameter. Parameters in the univariable analysis with $P \leq .2$ were included in the multivariable analysis; evaluable status = outcome reference.

[i]Not yet determined whether evaluable or inevaluable as of September 26, 2017.

Figure 1. Reasons for being inevaluable in the I-PREDICT trial (University of California, San Diego site)



SUPPLEMENTAL: MATERIALS AND METHODS

I-PREDICT Trial

The I-PREDICT trial is a prospective navigational trial that included subgroups with metastatic or locally advanced unresectable disease that were treatment naïve, albeit with lethal cancers, and patients who had exhausted treatment in the metastatic or unresectable setting.

Participants

To be eligible for the I-PREDICT trial, pertinent inclusion criteria included: (a) age ≥18 years; (b) incurable malignancy that was treatment naïve and with ≥50% 2-year mortality, or previously treated metastatic disease that had failed standard therapies or had no standard therapy; (c) measurable disease on cross-sectional imaging; (d) Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 [S1] and New York Heart Association Functional Class of I-II [S2]; (e) adequate end-organ (including bone marrow, liver and kidney) function; (f) able to swallow; (g) a negative pregnancy test for fertile women; and (h) no severe or uncontrolled medical disorder, for example, uncontrolled infection, diabetes, lung disease, psychiatric disorder, or kidney disease. The database was locked on September 26, 2017.

Molecular Profiling

Next-generation sequencing was performed using Foundation Medicine on blood and/or tissue (FoundationOne™, FoundationOne Heme™ and FoundationACT, Cambridge, Massachusetts, http://www.foundationmedicine.com) (clinical-grade, Clinical Laboratory Improvement Amendments (CLIA)-certified). The FoundationOne™ tissue assay interrogates 236 to 405 genes. All 4 classes of genomic alterations (base substitutions, deletions and

insertions, rearrangements, and copy number alterations) are recognized. FoundationACT is a blood-derived circulating tumor DNA assay that identifies 62 clinically pertinent genomic alterations.

Data Analysis

Comparisons of characteristics between groups were made by using the two-sample Pearson's chi-square test, Student's *t*-test, and Aspin-Welch *t*-test. Univariable and multivariable analyses with binary logistic regression modelling evaluated patient characteristics as independent predictors of inevaluable status. The subgroup of evaluable patients with previously treated metastatic or advanced cancers from the two study sites has been published [10]. The current analysis examines inevaluable patients derived from all consecutively enrolled patients in both the treatment-naïve and previously treated cohorts at the UC San Diego Moores Cancer Center.

Definition of Inevaluable Patients

Patients were considered "inevaluable treated" for the following reasons: (a) treated but early lost to follow-up ($\leq$10 days post therapy initiation); (b) received an oral drug daily for $\leq$10 days; (c) received less than 2 doses of an intravenous drug; (d) on trial for $\leq$10 days before death; (e) received inconsistent/intermittent treatment; (f) signed consent but then failed eligibility criteria for treatment upon protocol work up (but received a therapy of some type); (g) therapy was initiated over 6 months after consent; and (h) molecular profiling failed but the patient received a treatment of some type. Patients were considered "inevaluable untreated" for the following reasons: (a) never received any treatment after signing consent and over 6 months had elapsed from consent, if they were still alive; (b) died without receiving treatment; and (c)

patient refused treatment after initially consenting to the study. Patients who were not yet treated and for whom 6 months had not yet elapsed since consent were classified as "awaiting treatment." Patients awaiting treatment were not included in the analysis of inevaluable patients.

Supplemental References

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Supplemental Table 1. Tumor Types of Consented Patients in the I-PREDICT Trial (University of California, San Diego site)

Parameter	Evaluable	Inevaluable	Awaiting Treatment
Consented, *N* = 190	99 (52%)	83 (44%)	8 (4%)
Tumor type			
Blood, *n* = 3 (1%)	1 (33%)	2 (67%)	0
Breast, *n* = 5 (3%)	4 (80%)	1 (20%)	0
Central Nervous System, *n* = 7 (4%)	5 (71%)	2 (29%)	0
Endocrine, Neuroendocrine, *n* = 6 (3%)	3 (50%)	2 (33%)	1 (17%)
Gastrointestinal[a], *n* = 103 (54%)	50 (49%)	49 (47%)	4 (4%)
Genitourinary, *n* = 5 (3%)	3 (60%)	2 (40%)	0
Gynecological, *n* = 27 (14%)	13 (48%)	12 (45%)	2 (7%)
Lung, *n* = 3 (1%)	2 (67%)	1 (33%)	0
Mesothelioma, *n* = 2 (1%)	0	2 (100%)	0
Oral, Head, and Neck; *n* = 10 (5%)	6 (60%)	3 (30%)	1 (10%)
Soft Tissue Sarcoma, *n* = 18 (10%)	11 (61%)	7 (39%)	0
Unspecified site, *n* = 1 (1%)	1 (100%)	0	0

Note: Data for evaluable, inevaluable, and awaiting treatment are presented as *n* (%) of the tumor type.

[a]Gastrointestinal tumor type includes hepatobiliary (16%, *n* = 16 of 103 patients) and pancreatic cancers (12%, *n* = 12 of 103 patients).