Retrospective Study of the Predictive Value of Target Now® in Systemic Therapy for Metastatic Colorectal and Gastric Carcinomas

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ABSTRACT: **Background:** Predictive biomarkers for personalized treatment of neoplasms are suggested to be a major advancement in oncology and are increasingly used in clinical practice, albeit based on level II evidence. Target Now® (TN) employs immunostaining and RNA expression on tumor samples to identify potentially beneficial or ineffective drugs.

Objectives: To explore retrospectively the predictive value of TN for patients with colorectal and gastric carcinomas.

Methods: The study group comprised colorectal and gastric carcinoma patients with TN test reports. We identified chemotherapy regimens given for stage IV disease for which TN reports indicated prediction. Protocols were classified as having clinical benefit (CB; i.e., stable disease or any objective response) or progressive disease, and this was compared with the TN prediction.

Results: Nineteen patients – 12 colorectal and 7 gastric carcinomas – met the inclusion criteria. There were 26 evaluable treatment protocols; of 18 with a CB 15 were predicted to have a CB while 3 were predicted to have a lack of CB. Of eight protocols that had no CB, seven were predicted to have a CB and one a lack of CB. A chi-square test was non-significant ($P = 0.78$). An exploratory analysis yielded a positive predictive value of 68% and a sensitivity of 83% for the TN test.

Conclusions: This study emphasizes the need for larger multicenter studies to validate the TN test before it is adopted into clinical practice.

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Personalized medicine is advocated as the future in medicine [1]; perhaps it is already present. Choice of treatment is largely based on the results of studies at the population level, grouping together tumors of a single histological type but with immense diversity in molecular profiles and response to treatment. Recently however, some exceptions emerged. For example, drugs targeting HER2 (e.g., trastuzumab, pertuzumab, ado-trastuzumab emtansine) are prescribed based on the results of immunohistochemistry and fluorescent in situ hybridization of HER2 in breast and gastric carcinomas [2]. However, generally, tests for individual tumor sensitivity to chemotherapeutic agents are not widely accepted.

Recently, several tests have been developed alleging predictive capacity for choosing therapeutic regimens in cancer patients; one such test is Target Now® (TN, renamed Caris Molecular Intelligence) [3] which combines gene expression and immunohistochemistry. This test yields two categories of drugs: agents associated with clinical benefit or associated with lack of clinical benefit. The test draws from studies (mostly retrospective) testing individual biomarkers. For example, high expression of ribonucleotide reductase large subunit (RRM1) has been associated with lack of benefit of gemcitabine-based chemotherapies, and vice versa [4].

A single study was performed to validate this battery [5]. Patients with metastatic neoplasia (N=86) whose disease had progressed on multiple treatment regimens were treated according to the results of molecular profiling of their tumor. Progression-free survival with the study agent was compared to progression-free survival in response to the preceding "conventional" line of therapy. A ratio of 1.3 of these two measures was considered to indicate clinical benefit. From the study population, 18 of 66 patients treated based on an identified targetable marker (27%) met the criterion of a 1.3 ratio for progression-free survival.

The pressure from patients and regulatory agencies has led to the rapid adoption of new technologies in oncology, sometimes at the expense of rigorous validation. Thus, despite the lack of convincing randomized data, the TN test has been adopted in clinical use, but it is reserved mainly for patients in whom multiple treatment lines failed or who had unusual tumors for which there were no standard therapeutic guidelines.

In the current study we aimed to investigate retrospectively the contribution of TN data to patient management in the Sharett Institute of Oncology at the Hadassah-Hebrew University Medical Center and to extrapolate from this to general use of this test. Specifically, we explored the association between the therapeutic decision based on TN recommendations and clinical benefit (across all lines of treatment).

PATIENTS AND METHODS

A retrospective study was conducted at the Sharett Institute of Oncology at the Hadassah-Hebrew University Medical Center. Inclusion criteria were: adult patients of all ages suffering from colon or gastric cancer who were seen by a physician at our institute and for whom a TN report was available. The study was approved by the local institutional review board.

DATA COLLECTION AND ANALYSIS

The TN reports were reviewed, and data on agents noted to be associated with clinical benefit or lack of such benefit were gathered.

Patient charts with TN tests performed between September 2009 and January 2012 were reviewed and clinical data were extracted. Data included demographics, tumor histology and site, cancer-specific therapy administered (drugs used, start and end date, number of cycles), and response to therapy (based on imaging and clinical evaluation).

Each line of treatment was reviewed per patient and protocols were included in the analysis if any of the agents given was noted on each patient report to have either "Clinical benefit" or "Lack of clinical benefit." Time or line of treatment in relation to the time of TN analysis was disregarded, thus protocols were analyzed even when administered prior to TN testing. Protocols were excluded from analysis if they combined agents noted as having "Clinical benefit" with agents having "Lack of clinical benefit" on the TN report, as were protocols that led to a "mixed" tumor response.

Response to each protocol in the analysis was categorized as leading to clinical benefit (i.e., complete response, partial response, or stable disease) or lack of clinical benefit (i.e., progressive disease) based on the clinical data. Stable disease determination was based on imaging with an interval of not less than 2 months.

Data were encoded in a Microsoft Office Excel worksheet and statistical analysis was carried out using Statistica 8 software. For continuous variables data are reported as mean ± standard deviation. Statistical significance was ascertained using the chi-square test for qualitative variables. A *P* value of less than 0.05 was considered statistically significant

RESULTS

In a review of patients treated at our oncology institute, we identified 76 for whom TN testing was performed. Of these, 20 met the inclusion criteria for site of disease (colon or gastric); all had metastatic disease. One patient was excluded due to lack of clinical data (lost to follow-up). Final analysis was performed on 19 patients [Table 1]. All patients included in the study had a prediction on their TN report for at least one agent with which they were treated.

Patients received an average of 3.17 ± 1.18 protocols of systemic therapy for stage IV disease, leading to a total of 54 protocols. Of these, 2.23 ± 1.03 were administered prior to TN testing and the remainder following testing. Therapy protocols in which no agent had a prediction on the TN report were excluded (N=7). Further exclusion included: protocols with a mixed response (N=2), a combination of agents for which TN predictions were conflicting (N=15), missing response data (N=1), or combination protocols in which the agent for which a prediction was available (e.g., fluourouracil, 5-FU, in FOLFOX) had already been given (e.g., as part of a FOLFIRI protocol, N=3). Thus, the final analysis was performed on 26 therapy protocols (mean per subject 1.36 ± 0.95). Of these protocols, 61.5% were administered in treatment lines that actually preceded TN testing (N=16).

There were 18 protocols that resulted in clinical benefit (any response or stable disease) of which 15 were predicted to have a clinical benefit (10 of these had an objective response, 5 showed stable disease), while 3 were predicted to have a lack of clinical benefit (all with an objective response). Of eight protocols that had no clinical benefit, seven were predicted to have a clinical benefit and one a lack of clinical benefit [Table 2]. A chi-square test was non-significant ($P = 0.78$).

An exploratory analysis was performed. Based on these data the positive predictive value (i.e., the percent of protocols with a clinical benefit of all those with a clinical benefit predicted) of TN was calculated to be 68% and the sensitivity of the test (i.e., the percent of true clinical benefit predicted to be such based

Table 1. Characteristics of the study population

Total no. of subjects	19
Gender Male Female	 12 7
Age at diagnosis	49 ± 14 years
Time from diagnosis to TN testing Time from metastases to TN testing	46.44 ± 56.88 months (N=16) 18.7 ± 19 months
Primary tumor site Colorectal cancer Gastric cancer	 12 7
Evaluable treatment protocols	26, mean 1.36 ± 0.95

Table 2. Clinical benefit vs. Target Now prediction

		Clinical benefit		
		Yes	**No**	
Target Now prediction	**Clinical benefit**	15	7	PPV = 15/ (15+7) = 68%
	Lack of clinical benefit	3	1	
		SN = 15/ (15+3) = 83%		

SN = sensitivity, PPV = positive predictive value

Table 3. Relation between clinical benefit and Target Now prediction per therapeutic agent

Drug	Clinical benefit & benefit predicted	No clinical benefit but benefit predicted	Clinical benefit but lack of benefit predicted	No clinical benefit & lack of benefit predicted
Irinotecan	10			
Fluouropyrimidines	5	2		
Bevacizumab	4			
Oxaliplatin	2		1	1
Cetuximab	2		1	
Temozolamide	1	2		
Cisplatin	1		1	
Carboplatin	1			
Epirubicin	1			
Gemcitabine		1		
Mitomycin C		1		
Panitimumab	1			
Sunitinib		1		

on TN results) 83%. Due to the small number of protocols with a "lack of clinical benefit" prediction, negative predictive value and specificity were not calculated.

Of the protocols reported above, 10 were administered following TN testing reflecting the potential benefit for the specific patients studied. Of these, six were both predicted to and in fact led to clinical benefit (objective response in three and stable disease in three); four were predicted to lead to clinical benefit but did not.

Most of the treatments prescribed to patients in this study were standard-of-care agents [Table 3]. This reflects, in part, the fact that we included treatments administered prior to TN testing. Two unusual agents are temozolamide (TMZ) and sunitinib, which were administered based on TN recommendations to patients with colon cancer. Of three patients who received TMZ, one showed a clinical benefit; this case has been reported previously [6]. Treatment with sunitinib failed to produce clinical benefit in one patient.

DISCUSSION

This study aimed to test the predictive value of Target Now, a molecular tool for personalized medicine. We report a non-significant positive predictive value of 68% for clinical benefit and sensitivity of 83% for the test. This is an above-chance level that if corroborated in larger scale studies would provide support for use of this test.

While TN testing is often performed after failure of several lines of treatment (2.23 ± 1.03 in our sample), it should predict response to early lines of therapy assuming the test was performed on tissue collected prior to treatment initiation. In our study population, all but four protocols were administered following tissue collection submitted later on for Target Now analysis. Thus, we examined the association between clinical benefit and TN prediction across all lines of treatment given for stage IV disease. Indeed, correct predictions were frequent for standard lines of treatment usually prescribed early on in the course of the disease [Table 3]. The use of "non-standard" agents based on TN prediction was limited in our data set. This included temozolamide or sunitinib prescribed to four patients. One reason for this is the small number of treatments given following the test, due to progressive disease, poor condition, or death. Furthermore, when a more conventional treatment not yet employed was listed it was usually favored. Of the four patients mentioned above, one had a significant response to treatment. Considering the advanced line of treatment with few therapeutic options, this may be viewed as a meaningful result. Conversely, if indeed the molecular tests used are predictive of response, a higher rate of clinical benefit might be expected. Thus, it seems the current predictions should be considered auxiliary to decision making at best. This is also supported for example by the case of patient R.R. who had a complete response on a line of treatment (FOLFOX) predicted by the TN test to lack clinical benefit. Therefore, when an evidence-based line of treatment is available, it may be prudent to attempt treatment even in the face of a negative prediction in the TN report.

A significant shortcoming of TN lies in the report of single-agent associations. In metastatic disease the standard of care is often a combination regimen. TN provides no information regarding the effectiveness of combination therapy. It can hardly be assumed that the sum of predictions for each agent predicts the response to combination therapy. This is also a limitation of the current study since analysis was based on predictions of response to single agents while often there was no prediction for some of the agents in the combination protocol.

The present study reports the experience of a single center with a small sample size and thus lacked sufficient power to detect a statistically meaningful association. Recently Caris Life Sciences, the company behind TN testing, reported the launch of a registry of clinical data, treatments and outcome for patients tested [7]. This registry has the potential to provide large-scale validation of TN although independent reports such as our own have added value since they are sponsor independent. We further suggest that post-marketing collection of outcome data be obligatory for tests such as this, particularly in cases where clinical use preceded rigorous validation.

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