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Research Article

Clinical Utility of a ChemoFx® Drug Response Assay for Gynecologic Malignancies

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Abstract

Objective: To assess the utility of a chemoresponse assay (ChemoFx®) in planning for gynecologic malignancies.

Study Design: A retrospective chart review from November 2008 - July 2012 identified patients at 3 institutions with a tissue specimen sent to Precision Therapeutics for *in-vitro* chemosensitivity testing via ChemoFx®. Chemosensitivity testing was performed on tumors from 71 Patients with Uterine, Cervical, Ovarian and non- Gynecologic primary cancers. Tumors were classified as responsive (RR), intermediately responsive (IR), and nonresponsive (NR) to multiple chemotherapeutic regimens.

Overall survival based on treatment concordance and chemotherapy used was assessed using descriptive statistics and Kaplan Meier survival plots.

Results: There was a mean survival benefit for patients treated with RR (39.6 months) over IR (21.3 months) or NR (18 months) ($p = 0.03$). There was a trend towards significance ($p = 0.068$) of prolonged overall survival when C/T was RR when compared to those when C/T was IR or NR.

Conclusion: When prescribed accordingly, a responsive chemotherapy regimen on ChemoFx® is associated with an improved overall survival in patients with a gynecologic malignancy regardless of stage of disease, disease type, or residual disease.

Keywords: *Chemoresponse Assay; ChemoFx®; Gynecologic Malignancies; Responsive (RR); Intermediately Responsive (IR); Nonresponsive (NR)*

Introduction

Gynecologic malignancies account for > 11% of all female malignancies [1]. In total, they have an estimated incidence rate of 80,720 cases per year, making them the fifth leading cause of all cancer- related deaths in American women (after lung, breast, colorectal, and pancreatic cancers). Over the last 20 years, cytotoxic chemotherapy, radiation and surgery have improved outcomes for patients with gynecologic malignancies. Survival rates, however, have reached a relative plateau. This is in part, due to the emergence of drug resistance

against traditional therapies (and the frequent recurrence rate of gynecologic malignancies despite the use of neoadjuvant and/or adjuvant therapies). Ovarian carcinoma, for example, is the gynecologic malignancy associated with the highest mortality rate; it has a total estimated cure rate of only 30% [2]. This subset of patients have a particularly high risk of developing drug resistance and disease recurrence. Therefore, it is imperative that more effective, specific, and less-toxic approaches are developed in order to improve outcomes for patients with gynecologic malignancies.

At this point in time, there are no pre-defined clinical or histologic parameters that can accurately predict a patient's individual response to a given chemotherapy. Currently, the standard of care is defined based on NCCN guidelines and expert opinion. It makes sense then, that an *in-vitro* test capable of assessing tumor specific chemotherapeutic response has the potential to predict *in-vivo* response rates to both single agent and combination chemotherapies even before treatment initiation. The ability to identify a patient's chemospecific response status (responsive vs. non- responsive) is potentially beneficial for multiple reasons. It limits patient exposure to unnecessary treatments (and unwanted side effects) and identifies alternate therapies more likely to be effective in primary, progressive and recurrent disease. Most importantly, this patient specific care has the potential to improve treatment outcomes, both progression free and overall survival rates.

Many researchers have sought to develop *in vitro* methods that accurately predict the chemosensitivity of human tumors *in vivo*. Personalized chemotherapy is dependent on accurate assay methods, utilizing either molecular based predictive biomarkers or *ex vivo* evaluation of tumor chemosensitivity. Over the years, multiple chemosensitivity assays have been developed including the extreme drug resistance assay (formerly known as Oncotech, INC), the real time sensor-based platform [1], the ATP-based chemosensitivity assay, the histoculture drug response assay (HDRA), and the collaged gel droplet embedded drug sensitivity test. Each of these assays are associated with limitations and advantages. The HDRA, for example, was found to be incapable of identifying differences in chemosensitivity according to histopathology and FIGO stage and was later abandoned.

Currently, the leaders in patient and tumor specific targeted cancer therapy are Caris Target Molecular Profiling, which uses tumor specific biomarker analysis to personalize cancer therapy, and Precision Therapeutics ChemoFx®. In contrast to molecular profiling, ChemoFx® is a drug response marker [3,4]. It quantifies a patient's probable tumor response to various chemotherapeutic agents; information which can later be used to guide a patient's therapeutic course of action. The validity and potential benefit of ChemoFx testing has been demonstrated in multiple previous studies. Huh., *et al*. (2011) demonstrated chemotherapeutic response rates predicted by ChemoFx consistent with expected population response rates. Furthermore, studies have shown both a direct correlation between ChemoFx response rates and both progression free survival [5], as well as overall survival [6].

ChemoFx® was used in our multi-institutional study (due to the multiple innovative advantages it has over other similar testing strategies). It provides tumor specific information regarding both chemosensitivity and resistance, identifying chemotherapies more or less likely to be effective. This strategy potentially eliminates risks associated with ineffective chemotherapy administration, including tumor progression, unwanted side effects, systemic toxicity and the development of cross resistance. Additionally, ChemoFx® requires only a small amount of tissue for testing. A sample size greater than 34 mg (as much as two core needle biopsies) or 100cc of ascitic or pleural fluid is all that is required, saving patients from unnecessary, often invasive sampling procedures.

Within the Gynecologic Oncology departments at our three institutions (New York Methodist Hospital, Long Island College Hospital and SUNY Downstate Medical Center) all surgically derived tissue specimens are sent for ChemoFx® chemosensitivity testing at the discretion of the attending physicians. The benefit of utilizing such results in the treatment planning of our patients, however, is for the most part, unknown. This study was performed to assess both the utilization and potential benefit of Chemofx testing in the management of our population specific gynecologic oncology patients.

Materials and Methods

Institutional approval was acquired from each of 3 participating institutions. A retrospective chart review from November 2008 - July 2012 identified patients at 3 institutions with a tissue specimen sent to Precision Therapeutics for ChemoFx®. Data included patient demographics, cancer type, time to ChemoFx® result, chemotherapy prescribed, concordance with ChemoFx® results, response to treatment, and patient outcomes. Descriptive demographic and clinical data are detailed in table 1. Descriptive statistics and Kaplan Meier survival plots were used in the analysis.

ChemoFx drug-response marker

All surgically derived tissue specimens were submitted as per ChemoFx® protocol and received within 24 hours. Specimen-specific cell cultures were grown incubated with a panel of therapeutic drugs previously selected by the referring physician. Chemotherapy concentration was determined by drug specific sub-therapeutic, supra- therapeutic and expected (during treatment) serum blood levels. Dose-dependent response curves were used to illustrate post-treatment cell survival. Response to treatment was categorized as non-responsive (NR), intermediately responsive (IR), and responsive (R) according to the number of doses required to achieve a reduction in total cell survival of ≥ 35%.

Results

103 specimens from 97 unique patients were sent from our 3 institutions from November 2008 - July 2012. The majority of specimens (93.2%) submitted for cytological analysis were derived from explanted tumor tissue with only 7 (6.8%) specimens comprised of ascitic fluid. Precision results were available 33 +/- 10.4 days from surgery (range 15 - 80).

The study's final sample size consisted of 39 patients after all exclusion criteria were met. Exclusion criteria included availability of charts for review, cancer of non-gynecologic primary origin, patients who received RT with chemosensitization prior to surgery, those who declined treatment, had disease not requiring chemotherapy, and patients who received chemotherapy at outside institutions or were administered chemotherapeutic regimens not tested by ChemoFx®. Demographic and clinical data are detailed in table 1. Exclusion criteria and final sample size data are detailed in figure 1.

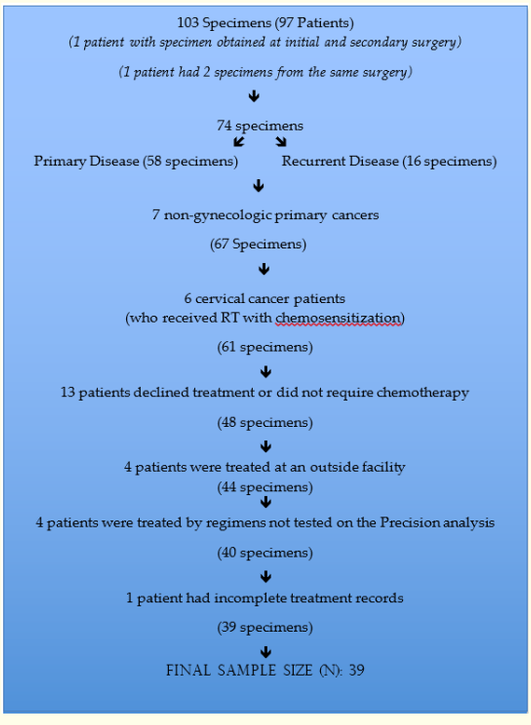

Figure 1: *Exclusion criteria and final sample size.*

Characteristics	N	(%)
Average patient age, Y (range)	63	32 - 90
Race		
Black	30	50
White	21	35
Other (Hispanic, Asian)	9	15
Cancer Type		
Ovarian	26	26/74
Papillary Serous	18	18/26
Endometrioid	5	5/26
Other	3	3/26
Uterine	35	35/74
Endometrioid	9	9/35
Papillary-serous	14	14/35
Carcinosarcoma	7	7/35
Other (Corpus Sarcoma)	5	5/35
Primary vs. recurrent disease and debulking status		
Primary Total	58	
Primary Optimal Debulking	35	
Primary Sub-Optimal Debulking	19	
Recurrent Total	16	
Recurrent Optimal Debulking	8	
Recurrent Sub-Optimal Debulking	7	
No Reported Status	5	

Table 1: *Patient demographics.*

A total of 39 patients met inclusion criteria. All eligible participant received at least 1 cycle of treatment and follow up care at one of our three institutions. Of these 39 patients, 18/39 (46.2%) were treated with responsive regimens, 8/39 (20.5%) with intermediate regimens and 13/39 (33.3%) with non-responsive regimens as determined by Precision Therapeutics. Chemotherapy was initiated before ChemoFx results were reported in 17 (43.6%) patients. Of these patients, 3 had recurrent disease. Despite starting treatment early, 10 (58.8%) were treated with a regimen that was responsive, 5 (29.4%) were treated with an intermediate response regimen, and 2 (11.8%) were treated with a resistant regimen. Of the 22 where Precision had resulted before treatment was initiated, 8 (36.4%) were treated with a responsive regimen, 3 (13.6%) were treated with an intermediate response regimen, 11 (50%) were treated with a non-responsive regimen. 5 of these patients had recurrent disease. These results are detailed in table 2.

	Recurrent Disease/Total	Responsive	Intermediate Response	Non-Responsive (Resistant)
Total (N = 39)	8/39	18/39 (46.2%)	8/39(20.5%)	13/39 (33.3%)
Number of patients in whom treatment was initiated before Precision results were reported	3/17	10 (58.5%)	5 (29.4%)	2 (11.8%)
Number of patients in whom treatment was initiated after Precision results had been reported	5/22	8 (36.4%)	3 (13.6%)	11 (50%)

Table 2

Overall survival based on concordance of treatment

There was a mean survival benefit for patients treated with a responsive (39.6 months) over an intermediate regimen (21.3 months) or non-responsive regimen (18 months) ($x^2(2) = 7.023$, $p = 0.03$). See figure 2.

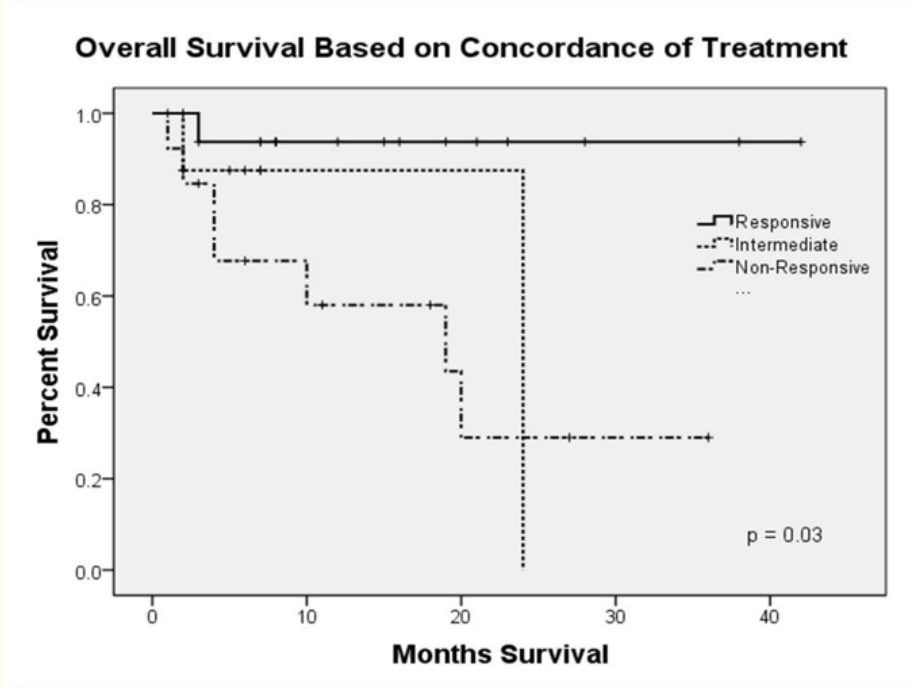

Figure 2

Overall survival: Carboplatin/taxol as primary regimen

One rationale for why providers may not use the ChemoFx® results would be that it was not standard of care. Therefore, we examined the patients who received carboplatin and paclitaxel as initial treatment (n = 23) and examined the overall survival of patients based on debulking status, disease type, stage, and ChemoFx® results.

When looking only at primary disease originally treated with carboplatin and paclitaxel, there was not a significant difference in overall survival based on optimal or sub-optimal debulking status ($x^2(2) = 0.375$, $p = 0.540$), primary disease type (ovary versus endometrial) ($x^2(2) = 0.054$, $p = 0.816$), or stage of disease ($x^2(2) = 0.374$, $p = 0.830$). There was a trend towards significance ($x^2(2) = 5.377$, $p = 0.068$) of prolonged overall survival for those treated with a responsive regimen when compared to those treated with an intermediate or non-responsive regimen (Figure 3). There were no deaths in the group treated with a responsive regimen (0/12), 2 deaths in the intermediate regimen (2/5) and 2 deaths in the non-responsive regimen (2/6). When grouping intermediate and non-responsive regimens together and comparing them to responsive regimens, there was a significant overall survival benefit for those treated with a responsive regimen ($x^2(1) = 4.741$, $p = 0.029$).

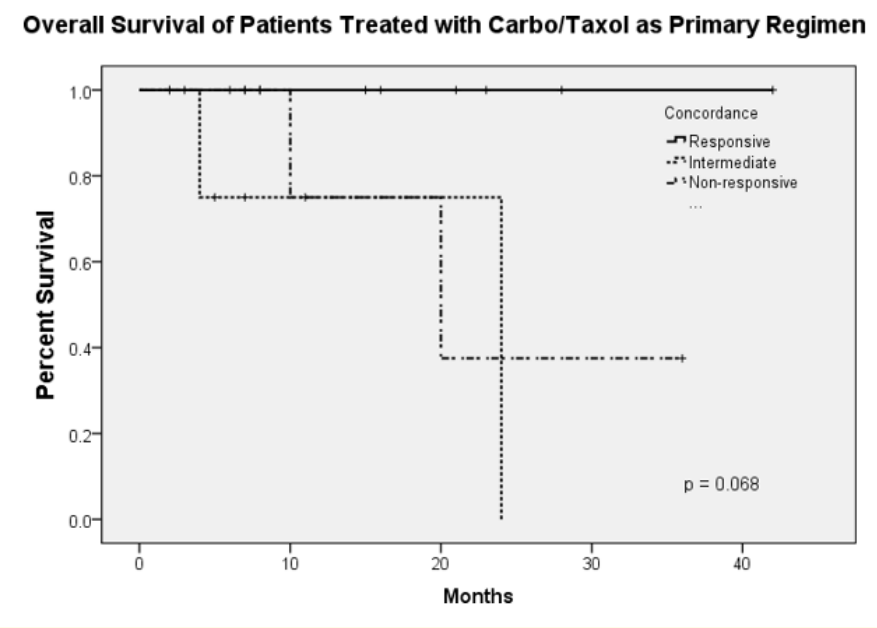

Figure 3

There was not a significant difference between the three regimens with regards to current disease status ($x^2(2) = 2.232$, $p = 0.328$).

Discussion

This study highlights several important questions, namely: the standard of care is a term used to describe evidence based, consensus driven management of patients with a particular cancer. Guidelines ensure patients are treated according to what is most likely to lead to optimal outcomes [7]. In our study, treatment was initiated after ChemoFx® results in 22 of 39 Patients. 50 percent, however, were treated with a non-responsive regimen. This brings up several issues. At what point will a physician deny a patient the standard of care in order to administer a chemotherapeutic regimen showing a more favorable response rate via Chemosensitivity studies?

Currently, only retrospectives studies have correlated ChemoFx® results with cancer-free survival in patients with gynecologic cancers [7-9]. Naturally, these studies had major limitations including selection and observational biases, lack of control groups, blinding or randomization (chemotherapeutic regimens were chosen by the treating physician). The ChemoFx® assay has not been prospectively compared to other molecular or cellular assays meant for chemosensitivity testing. Furthermore, it has not been compared to the clinical gold standard. According to 2012 NCCN guidelines, there are situations in which assays like ChemoFx® may be appropriate; a case in which multiple equivalent chemotherapeutic options are available for a patient, for example, may represent such a scenario. The current evidence available is category 3 however, and it is not sufficient to supplant the chemotherapeutic standard of care. In sum, the ChemoFx assay is investigational. Peer-reviewed, randomized, controlled studies are needed to determine if the ChemoFx® assay can identify patient specific chemotherapies with improved side effect profiles, greater efficacy when compared to the standard of care, or improved patient outcomes using individualized regimens in place of the standard of care. In the setting of non-concordant chemosensitivity results, physicians will be able to make better treatment choices only once prospective studies in this area have been completed.

Conclusion

When prescribed accordingly, a responsive chemotherapy regimen on ChemoFx® is associated with an improved overall survival in patients with a gynecologic malignancy regardless of stage of disease, disease type, or residual disease. Prospective studies to evaluate use of ChemoFx® to determine optimal initial chemotherapy after primary surgery should be investigated.

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