MOLECULAR PROFILING IN RECURRENT OVARIAN CANCER PATIENTS: CONSIDERATIONS FOR THE DESIGN OF CLINICAL STUDIES TO VALIDATE PROFILING FOR THERAPY SELECTION

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BACKGROUND AND RATIONALE

Ovarian cancer is the most lethal gynecologic malignancy. In 2010, 21,860 women were diagnosed with ovarian cancer and 13,850 died of this disease (est. American Cancer Society, Cancer Facts & Figures 2010. Atlanta: American Cancer Society; 2010). Most patients are diagnosed with advanced stage ovarian cancer respond to first-line, standard-of-care platinum-based therapy, but >75% of these patients recur. Therapies for recurrent patients are often empirically selected and usually include taxanes, gemcitabine, anthracyclines, topotecan or other topoisomerase inhibitors, and occasionally fluoropyrimidines and anti-folates (see Table 1). However, limited response or short duration of response are unfortunately observed with all of these agents. Thus, there is a critical need for rational approaches that identify which drugs have the greatest chance to be effective in each individual patient.

Our goal is to improve patient outcomes by enabling selection of chemotherapies based upon individual tumor molecular profiles. Achievement of this goal will require randomized clinical trials designed from hypothesis-generating data sets that characterize expression of candidate molecular markers. In order to identify the markers to include in such profiling, we performed a literature search for evidence supporting the association between biomarkers and clinical responses to drugs currently employed in ovarian cancer treatment and initiated expression studies of those markers in ovarian tumors. By determining expression characteristics of these markers in a large cohort of ovarian tumors, expression cut-points for future retrospective or prospective studies can be derived. In addition, evaluation of marker expression in specimens obtained from primary diagnosis as well as recurrent tumors would clarify the need for recurrent tumor specimens.

MATERIALS AND METHODS

Biomarker reference library generation. A survey of the PubMed database was undertaken to identify all reports that correlated biomarker expression data with clinical response (i.e., response/outcome, survival, overall survival). Following specific chemotherapeutic. The terms used were “drug” (i.e., paclitaxel and “marker” (i.e., Ki-67) and any drug biomarker combination that characterized a defined clinical response. The term “drug” was used to denote the agent used in a defined drug treatment “combination,” where the marker was identified as having potential correlation with any of the drugs involved. Initial searches recovered ~120,000 abstracts that met this criterion. Following a reference manager program. EndNote, each abstract was annotated to reflect cancer type, treatment, drug combinations used, clinical predictive ability, and marker type present. Filter, a database was created that contained specific biomarkers and the corresponding sample data. The use of a drug treatment “combination” excluded the presence of specific drugs cannot be assigned based on these biomarkers and expression cut-points.

Expression of chemotherapy response markers is variable in ovarian serous carcinomas (Figure 3). The overall marker profiles in primary and recurrent ovarian tumors are remarkably similar. However, expression of individual markers such as POG, TOP1, and RRM1 were significantly different in primary and recurrent lesions (Table 3 and Figure 4).

SUMMARY AND CONCLUSIONS

1. Biomarkers that have reproducibly significant associations with chemotherapy response (see Table 3) and are employed in ovarian cancer treatment were identified from a large cohort of ovarian tumors (Figure 5A). Use of these cut-points permits the stratification of 73% of the patients tested (Figure 5B).

2. Expression levels of three key biomarkers (i.e., POG, RRM1, and TOP1) analyzed in 46 primary and recurrent serous ovarian carcinoma specimens demonstrated significant differences between the two sample cohorts. The feasibility of using similar expression cut-points in other tumor types may be performed to further validate these results.

3. Using a percentile-ranking strategy to score tumors for expression of a subset of these chemo-response predictive markers, 73% of the patients could be assigned to chemotherapy, although additional clinical validation of the results are still required. These results demonstrate, however, the feasibility of using similar expression cut-points for patient stratification for prospective clinical trials.

4. Future studies should incorporate the additional markers identified by the meta-analysis (see Table 1) into the marker testing panel and increase the size of the patient cohort in the analysis.

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Figure 1. Biomarker references (library) and associated cut-points.

Table 1. Chemotherapies and Associated Response Biomarkers

Table 2. Clinical Characteristics of Ovarian Serous and Adenocarcinomas Patients and Specimens Used in This Study

Table 3. Chemotherapies and Associated Response Biomarkers

Figure 2. Prevalence and reproducibility of expression of markers associated with chemotherapy response.

Figure 3. Expression of chemotherapy response markers in variable in ovarian serous carcinomas. (A) The overall marker profiles in primary and recurrent ovarian tumors are remarkably similar. However, expression of individual markers such as POG, TOP1, and RRM1 were significantly different in primary and recurrent lesions (B and C).

Figure 4. Expression cut-points for the chemo-response biomarkers identified in our survey of published clinical research can be proposed based on this analysis of 46 tumor specimens (Figure 5A). Use of these cut-points permits the stratification of 73% of the patients tested (Figure 5B).