Drug Efflux Pump Expression in 50,000 Molecularly-Profiled Cancer Patients

[1]Rebecca Feldman, PhD, [1]Sandeep Reddy, MD, [1]Brian Abbott, MD, [2]Michael Castro, MD
[1]Caris Life Sciences, Phoenix, AZ, [2]Queen's Medical Center, Honolulu, HI

Abstract (No. 11108)

Background: The multidrug resistance (MDR) phenotype reduces the efficacy of various chemotherapies. MDR is linked to the overexpression of ATP-binding cassette (ABC) transporters in cancer cells, including P-glycoprotein (PGP/ABCB1), multidrug resistance protein (MRP1/ABCC1) and breast cancer resistance protein (BCRP/ABCG2). We assessed protein expression patterns of the drug efflux pumps across all tumor types for insight on how to exploit MDR status to circumvent treatment dilemmas.

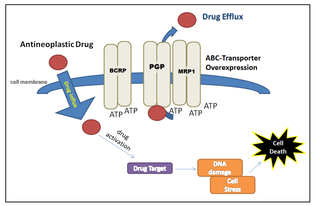
Methods: 51,939 patients molecularly profiled with a commercial multiplatform approach (Caris Life Sciences) were evaluated. Protein expression by IHC was assessed. The Caris Registry was queried for patients in this analysis with available clinical outcomes.

Results: Across all tumors profiled (n=51,939), MRP1 positivity (pos.) was highest at 81% (19935/24682), BCRP at 66% (8849/13409) and PGP the lowest at 23% (11969/51313). GI cancers exhibited the most abundant expression of all three drug pumps (80%, 90%, 53%), with highest average combined expression observed in liver cancers (81%). In contrast, brain, thymic and head and neck cancers exhibited the lowest average combined expression of all 3 drug pumps (39%, 40% and 42%, respectively). 6,002 patients were evaluable for co-expression with 29% (1728/6002) exhibiting pos. for all 3 drug pumps (ABC+) (highest frequencies in colon, pancreas, ovary, breast and lung), 42% (2494/6002) pos. for 2/3 drug pumps and 21% (1263/6002) pos. for 1/3 drug pumps. Only 9% (517/6002) exhibited negative status for all 3 drug pumps (ABC-) (highest frequencies in breast, lung, ovary, skin and endometrial). To determine the prognostic role of the drug pumps on patient survival, we assessed the differences in median survival between a cohort of ABC+ (n=30) and ABC – (n=27) patients with breast (n=6, 2), ovary (n=12, 6) and lung cancers (n=13,19). Median survival since specimen used for profiling was collected for ABC + was 596 days compared to 855 days for ABC – patients.

Conclusions: Tumors show broad and overlapped expression patterns for drug efflux pumps. Further study is needed to determine how transporter expression may impact clinical outcomes (e.g. ABC - status is more favorable than ABC + status).

Background

- Drug resistance is a major impediment to effective treatment with antineoplastic agents
- Tumors can be intrinsically resistant prior to chemotherapy or resistance can be acquired during treatment
- Multidrug resistance, or MDR, is the cross –resistance to many agents
- MDR transporters show broad and overlapped specificity for substrates



ABC Transporter	List of Chemotherapies that are substrates for drug pumps
PGP (ABCB1)	doxorubicin, daunorubicin, epirubicin, colchicine, antinomycin D, etoposide, teniposide, methotrexate, mitocycin C, paclitaxel, mitoxantrone, docetaxel, vinblastine, vincristine
MRP1 (ABCC1)	doxorubicin, daunorubicin, colchicine, topotecan, irinotecan, SN-38, methotrexate, etoposide, teniposide, vincristine, vinblastine, imatinib, gefitinib
BCRP (ABCG2)	doxorubicin, daunorubicin, epirubucin, methotrexate, topotecan, irinotecan, SN-38, etoposide, teniposide, imatinib, gefitinib

Adapted from Choi, et al. (2014). "ABC Transporters in Multidrug Resistance and Pharmacokinetics, and Strategies for Drug Development." Current Pharmaceutical Design. 20:793-807.

Methods

Patients molecularly profiled with a commercial platform (Caris Life Sciences) from 2009-2014 were assessed retrospectively, for PGP, MRP1 and BCRP expression data by immunohistochemistry. 51,939 patients were identified as having IHC expression profiles for at least one of the drug efflux pumps. Antibodies used included: PGP (C494), BCRP (6D171) and MRP1 (33A6). IHC thresholds (positive = ≥1+ and ≥10%) were used, based on predictive literature evidence. Slides were scored manually by board-certified pathologists, and results were reported as percentage of tumor cells that stained positive and intensity of staining (0, 1+, 2+, and 3+). Expression data are represented as percent positive frequencies or histoscores (i.e., product of percentage positive tumor cells and intensity). Patients referred to Caris Life Sciences® between 2009 and March 2014 were enrolled in the Caris Registry™. This IRB-approved registry includes baseline clinical information at the time of CMI™ testing, CMI™ results, treatments received and clinical outcomes including progression-free and overall survival updated at nine-month intervals after enrollment.

Results

Patient & Tumor Characteristics

Mean Age: 59 years

Tumor Type	n	Tumor Type	n	Tumor Type	n
Ovarian	9903	Melanoma	2140	Prostate	525
Breast	7623	Brain	977	SCLC	425
NSCLC	6532	Esophageal	687	Liver	342
Endometrial/Cervical	5277	Biliary Tract (gallbladder, bile duct)	650	Small Intestine	300
Colon/Rectum	5202	Stomach	630	Thyroid	225
Pancreas	3245	Head & Neck	618	GIST	200
Sarcomas	1752	Bladder	570	Thymus	150
Neuroendocrine	1588	Kidney	555	Uveal Melanoma	135

Table 1. Number of patients included in distribution analyses according to tumor type.

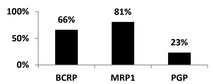


Figure 1. Percent positive expression of drug pumps in 51,939 tumors profiled. n=13,409 for BCRP, n=24,682 for MRP1, n=51,313 for PGP. MRP1 was the most frequently expressed drug pump, whereas, PGP was the least often found to be positive.

Results, continued

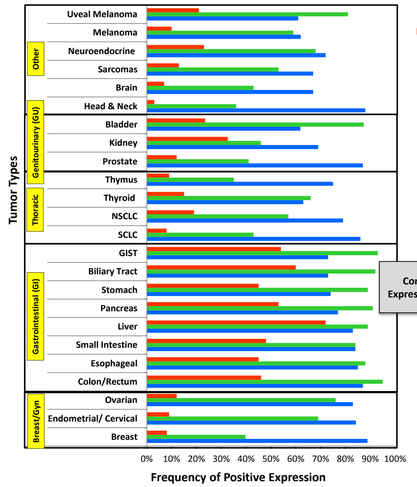


Figure 2. Distribution of positive expression rates, according to tumor type. PGP exhibits the most limited frequency of expression (red bars) across tumor types, compared to MRP1 which was most abundantly expressed (blue bars). GI cancers exhibited the most abundant overexpression of all 3 drug pumps.

Combined Expression Rates

Tumor Type	frequency
Liver	81%
Colon/Rectum	76%
Biliary Tract	75%
Pancreas	74%
GIST	73%
Esophageal	73%
Small Intestine	72%
Stomach	69%
Bladder	58%
Ovarian	57%
Neuroendocrine	54%
Uveal Melanoma	54%
Endometrial/ Cervical	54%
NSCLC	52%
Kidney	49%
Thyroid	48%
Prostate	47%
SCLC	46%
Breast	46%
Sarcomas	44%
Melanoma	44%
Head & Neck	42%
Thymus	40%
Brain	39%

Table 2. Combined expression rates of PGP, BCRP and MRP1, according to tumor type, and in order of decreasing frequency. Liver tumors exhibit the highest combined expression of drug pumps, and brain tumors, the lowest.

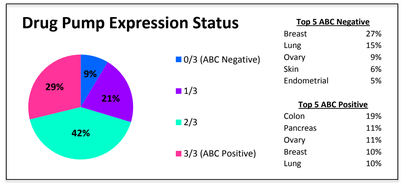


Figure 3. Patterns of Expression for BCRP, MRP1 and PGP. Only 9% of patients tested exhibited lack of drug pump expression, compared to 29% of the patients tested exhibiting co-expression of all 3 drug pumps. The majority of patients (63%) exhibit some degree of drug pump expression.

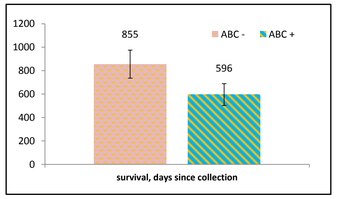


Figure 4. Differences in survival in ABC – (negative for BCRP, MRP1 and PGP) and ABC + (positive for BCRP, MRP1 and PGP). 57 patients from the Caris Registry, identified as being ABC- or ABC + displayed a difference in median survival (not statistically significant; p=0.4, error bars indicate standard error). ABC+ (n=30) and ABC – (n=27) patients with breast (n=6, 2), ovary (n=12, 6) and lung cancers (n=13,19).

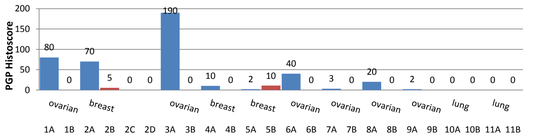


Figure 5. Expression of PGP in paired samples. Eleven patients identified from the Caris Registry were examined for changes in PGP expression in paired samples. 1-11 represents patients, A-D represents sequential PGP expression results and histology is represented above the patient number. Blue bars are from initial tumor profiling, red bars are from recurrent tumors. This data highlights the dynamic expression of drug transporters in cancer patients.

Case Report: Ovarian cancer patient (patient 3 in Figure 5) diagnosed with mixed serous and clear cell adenocarcinoma in 2001 undergoes total abdominal hysterectomy. Over the course of 8 years, patient undergoes treatment with multiple rounds of chemotherapy : paclitaxel + carboplatin, docetaxel + carboplatin, gemcitabine, docetaxel + carboplatin, docetaxel and altretamine. Upon recurrence in 2009, patient's illiac lymph nodes, positive for metastatic stage IV ovarian cancer were sent to Caris for tumor profiling, patient exhibited ABC + status : BCRP + (180), PGP + (190) and MRP1+ (130). Patient was treated with erlotinib (on trial) and obtains disease stabilization for 10 months. In 2010, the patient recurs with cutaneous metastasis; skin specimens were sent for Caris tumor profiling. The metastatic tumor specimen retained expression of BCRP + (195), however, lost expression of PGP (0) and MRP1 (0). Intriguingly, BCRP is a well-known transporter of tyrosine kinase inhibitors including erlotinib. Based on Caris profiling, the patient undergoes additional rounds of therapy including bevacizumab, paclitaxel + carboplatin and paclitaxel monotherapy. Patient survived an additional 7 months after profiling of third recurrence.

Conclusions

- Human cancer shows broad and overlapped expression patterns for drug efflux pumps. The identification of these biomarkers can be used to assess the likelihood treatment benefit for a variety of xenobiotic chemotherapy agents and stratify which treatment options are likely to provide the best chance for disease control in individual patients.
- The identification of these pumps could provide for a basis for targeted use of strategies to block this form of drug resistance in selected patient populations.
- Additionally, the use of xenobiotic-containing regimens for patients who lack all three pumps represents a potentially viable strategy of precision medicine. Further study is warranted to determine how transporter expression may impact clinical outcomes and contribute to chemotherapy resistance for particular chemotherapeutic agents.

References

1. Choi, Y.C. and A.-M. Yu, et al. (2014). "ABC Transporters in Multidrug Resistance and Pharmacokinetics, and Strategies for Drug Development.

Study Contact: rfeldman@carisls.com