Predictive biomarkers for chemotherapies in pancreatic cancer

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ABSTRACT

Pancreatic cancer is associated with high rates of mortality especially due to advanced stages of diagnosis. Adjuvant chemotherapy role is thus essential in the attempt to down-stage the tumoral grade. In cases of locally advanced tumors, this step could be followed by curative surgical resection. Characterization of predictor biomarkers for adjuvant chemotherapy has drawn increasing interest in molecular biology research of pancreatic cancer. Personalized treatment is one of the solutions proposed for advancing towards a better outcome. In this paper we discuss available predictor biomarkers with focus upon gemcitabine and FOLFIRINOX (5-fluoro uracil (5-FU), irinotecan and oxaliplatin) chemotherapy regimens, present approaches in advanced pancreatic cancer. Many data are current available in relation with gemcitabine chemotherapy regimen, where biomarkers like ribonucleotide reductase large subunit (RRM1), human equilibrative nucleoside transporter-1 (hENT1), deoxycytidine kinase (dCK), human antigen R (HuR), and secreted protein acidic rich in cysteine (SPARC) were proposed. Regarding the response to FOLFIRINOX components, other markers such as thymidylate synthetase (TS), topoisomerase I, and excision repair cross-complementation 1 (ERCC1) or KRAS mutation status were also investigated.

Key words: pancreatic cancer, chemotherapy, response predictor, biomarker

BACKGROUND

Pancreatic cancer is the fourth leading cause of cancer-related mortality (1) in developed countries and it is expected to become the second one (2). Increased mortality in this pathology is mainly related to the advanced stages at diagnosis, cases in which practically the moment for curative resection has been already exceeded (3).

A predictive biomarker is a specific biologic feature associated with the likely probability of benefit with treatment (i.e. chemotherapy). Starting from evidence obtained in other types of cancer, it was formulated the hypothesis of increasing chemotherapy's efficiency in pancreatic adenocarcinoma by the use of predictor biomarkers in an attempt to anticipate the response to adjuvant

therapy (4). Hence, the development of predictive biomarkers for the characterization of specific subsets of patients in pancreatic cancer is one of the important issues in current consensus reports on pancreatic cancer (5).

We intend to shortly review here the research findings on the influence of predictor biomarkers upon response to treatment of the main adjuvant therapies used for advanced pancreatic cancer, gemcitabine regimen and FOLFIRINOX (Folinic Acid, 5- fluoro uracil (5-FU), Irinotecan, and Oxaliplatin) regimen chemotherapy. We started our work with a Medline search using related keywords (i.e. pancreatic cancer and predictive biomarker, gemcitabine, irinotexan, oxaliplatin, 5-FU) with focus on data related to clinical data.

GEMCITABINE RESPONSE PREDICTORS

Gemcitabine is a nucleoside analogous used in adjuvant chemotherapy for pancreatic cancer. The efficiency of gemcitabine is not guaranteed when applied in unselected pancreatic cancer patient as resistance to gemcitabine may occur in some of the treated patients also (6).

The ribonucleotide reductase large subunit (RRM1) participates to the regulatory processes of cell proliferation, migration and also synthesis of deoxyribonucleotides, hence it can be a possible important component in tumor growth process. The RRM1 is actually possible cellular target for gemcitabine and its value as predictor for the response to this chemotherapy was studied in different neoplasia such as lung, breast, biliary tract, pancreatic cancer included (7). The RRM1 is actually an intracellular target for gemcitabine, so it was proposed as useful biomarker in pancreatic cancer (8).

The levels of RRM1, human equilibrative nucleoside transporter-1 (hENT1) or deoxycytidine kinase (dCK), were not shown to be predictive for survival in pancreatic cancer patients without adjuvant chemotherapy (9). But, in patients treated with gemcitabine, the presence of elevated in situ RRM1 expression was associated with significantly better overall survival than in patients with low RRM1 (6). The research results are however not uniform, since there are some other authors that did not approve the RRM1 use as a predictive biomarker in pancreatic cancer (10).

Human equilibrative nucleoside transporter-1 (hENT1)

The nucleoside-derived molecules like gemcitabine need transmembranary transportation in order to

transform into an active drug. This explains how hENT over expression produces an enhanced gemcitabine action in vivo (11).

According to its properties, the nucleoside transporter hENT1 is one of the predictor biomarkers in the pancreatic cancer (8). Upon multivariate analysis models, both hENT1 and dCK levels were independent predictors of survival after gemcitabine treatment (9). Also, both hENT1 and human nucleoside transporter 3 levels seem to be useful in predicting survival in pancreatic cancer patients treated by gemcitabine (12). On the contrary, the hENT1 expression in pancreatic cancer advanced metastasis is not associated with overall survival after pancreatic cancer (13). Other authors reported that the correlations made between hENT1 and survival in pancreatic cancer (i.e. low expression, associated with worse outcome) is independent of gemcitabine therapy (14).

In a prospective randomized trial that included 538 patients with pancreatic cancer, the increased hENT1 presence was associated with better outcome, overall and disease-free survival only in those undergoing gemcitabine therapies, but not when chemotherapy with 5-FU was applied (15). These data outlined the need for personalized treatment in pancreatic cancer (16), but still, obtaining an accurate method for hENT1 determination in daily practice requires further research (17). It was so also inferred that in pancreatic cancer, the gemcitabine regimen should not be indicated as adjuvant chemotherapy in patients with low hENT1 expression (18).

Deoxycytidine kinase (dCK) and human antigen R (HuR)

Human antigen R (HuR) is a RNA-binding protein associated with dCK involved in the metabolism followed by activation of the gemcitabine molecule. The HuR over expression leads to enhanced dCK protein presentation and plays an important role in the gemcitabine effect upon the tumor cells (19).

The HuR seems to be involved in the regulation of the pancreatic cell phenotype in critical states such as glucose deprivation, in facilitating the cellular survival in an impaired environment (20). The HuR expression is correlated with the tumor T stage and also a predictor of outcome in resected pancreatic cancers (21).

Secreted protein acidic and rich in cysteine (SPARC)

Secreted protein acidic and rich in cysteine (SPARC), albumin-binding protein, is associated with cells' migration and differentiation; all of which are processes

playing a key role in oncogenesis (22). The results of a study that included patients with metastatic pancreatic adenocarcinoma treated with maximum-tolerated doses of gemcitabine plus nab-paclitaxel showed that the SPARC expression was independently associated with the overall survival in multivariate regression models that included as covariates the sex, race, age, treatment, and baseline CA19-9 level. Even so, significant correlation was obtained only for the stromal SPARC and not for the SPARC expression in the tumor cells (23).

In regard with the data presented above, pancreatic tumors with low hENT1 and high RRM1 expression might be considered for chemotherapy regimens that include gemcitabine in future consensus statements. But also, further research is needed in order to validate this information and to improve the knowledge of the other biomarkers proposed as predictors in pancreatic cancer.

FOLFIRINOX

FOLFIRINOX, chemotherapy regimen including folinic acid, 5-FU, irinotecan and oxaliplatin, is used in advanced pancreatic cancer where a surgical resection is not suitable due to the advanced loco-regional disease. The purpose is to obtain in a neoadjuvant setting the tumoral down-staging in order to increase the pancreatic adenocarcinoma resectability rates.

After proving efficiency in pancreatic cancer (24, 25), the FOLFIRINOX was tested versus gemcitabine in a randomized trial with good results on survival rates. However, the improvement on the overall survival was grievd by the cost of increased toxicity (26).

FOLFIRINOX was observed to have greater efficiency in female patients and within the presence of high serum CA 19.9 levels (27). In this respect, it is to be noted that the current use of CA19-9 is for diagnostic and prognostic ends and not as a response predictor biomarker. For the moment, there are no data available on other predictor biomarkers for the FOLFIRINOX regimen, but efforts are done in order to identify targets for the individual chemotherapies with this regimen.

5-FLUORO-URACIL (5-FU) RESPONSE PREDICTORS

Deoxycytidine kinase (dCK) and human antigen R (HuR)

After exploring their utility as predictors of the gemcitabine treatment response, in a randomized

clinical trial in which pre-operative samples of pancreatic cancer were analyzed, it was found that the expression of both dCK and HuR is strongly correlated. Moreover, the dCK levels were predictive for the response to 5-FU (28).

Thymidylate synthetase (TS)

Thymidylate synthetase (TS), enzyme involved in the DNA synthesis processes, is a target in the chemotherapy with 5-FU. In 131 patients with pancreas adenocarcinoma the TS expression was explored in all cases. The rates of survival were similar between patients with low TS expression when compared with those with high TS expression in patients with palliative treatment. On the contrary, after pancreatic resection, the intensive chemotherapy was followed by a better outcome in patients with low TS expression (29). Not only for the pancreatic adenocarcinoma, but also in other cancers, the low TS expression was positively correlated with a better outcome (30).

In another research, the response to S1 – based chemotherapy was tested in the pancreatic cancer (31). The S-1, dihydropyrimidine dehydrogenase inhibitory fluoropyrimidine, is an oral adjuvant chemotherapy obtained by the modulation of 5-FU (32). The TS, dihydropyrimidine dehydrogenase (DPD), and orotate phosphoribosyltransferase expression was searched in 106 patients with pancreatic cancer. Among the three markers, DPD was the best predictor marker for the S1-based chemotherapy (31).

IRINOTECAN RESPONSE PREDICTORS

Irinotecan is a plant alkaloid classified as a topoisomerase I inhibitor that proved efficient in chemotherapy regimens for advanced pancreatic cancer.

Topoisomerase I

In patients with metastatic colorectal cancer, irinotecan was administrated when topoisomerase I expression was positive, and oxaliplatin was administrated in patients with negative topoisomerase I and positive ERCC1 expression, but this study did not find significant benefits on the overall survival (33). Still, we do not have yet evidence of the topoisomerase I expression relevance in pancreatic cancer; this will probably be a new research area in pancreatic cancer predictors.

OXALIPLATIN RESPONSE PREDICTORS

Oxaliplatin (trans-I-1,2-diaminocyclohexane oxalato-

platinum) is an antineoplastic platinum derivate with a 1,2-diaminocyclohexane carrier ligand (34) that showed anti-neoplastic effects against different pancreatic tumoral cell lines, PMH2/89 and fresh liver metastases secondary to pancreatic neoplasia included (35).

Excision repair cross-complementation 1 (ERCC1)

The excision repair cross-complementation 1 (ERCC1) is a key regulatory enzyme with expression related to the survival in several cancers (36), pancreatic cancer included. It was also proposed as a response predictor marker for the adjuvant chemotherapy in pancreatic cancer (37). The increased expression of excision repair cross-complementation 1 (ERCC1) in resected pancreatic cancers seems to be associated with lower recurrence-free interval rates and worse overall survival (38).

ERLOTINIB RESPONSE PREDICTORS

Excision repair cross-complementation 1 (ERCC1)

The cases in which a higher ERCC1 staining pattern was observed had better responses to the erlotinib associated with the combination gemcitabine – oxaliplatin (39).

KRAS mutation status

The hypothesis that genetic background could characterize subsets of pancreatic cancer patients sensitive to certain drugs introduced the possibility of personalized chemotherapy in cancer patients according to gene expression (40). The KRAS mutation status in patients with pancreatic cancer treated with erlotinib was found to be related with the overall survival even if not in correlation with the response to the adjuvant chemotherapy (41).

Thus, until now less is now about possible predictor biomarkers in rapport with each therapeutic principle of FORFIRINOX regimen and nothing in regard with a predictor for the response to the entire chemotherapeutic regimen.

CONCLUSIONS

The knowledge in the molecular biology of the pancreatic cancer is advancing. Hypothesis on the possible treatment options starting from the tumor molecular biology data are starting to be defined. In this respect, it seems that chemotherapy regimens based on gemcitabine do not have efficiency in pancreatic

tumors that present low hENT1 expression.

We presented in this paper also researches that has low level of evidence, as in this moment large clinical trials are lacking. There is so certainly need for further research in this field; but there is also hope that the advances in developing personalized treatment strategies will improve the outcome, the overall survival and the disease-free survival in a dreadful disease like the pancreatic adenocarcinoma.

Conflict of interest

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