

# The Human Equilibrative Nucleoside Transporter Protein1 (Hent1) is a Predict /Prognostic Factor in Resected Pancreatic Cancer Patients



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## Abstract

Pancreatic cancer is currently one of the deadliest of the solid malignancies and has a particularly low survival rate in the future because targeted therapies for other cancers are becoming more advanced than those for pancreatic cancer [1]. The optimal treatment first and foremost depends on careful accurate staging. The American Joint Committee on Cancer (AJCC) staging system, which includes the TNM classification, is the most widely used system to stage pancreatic cancer [2]. Patients with Stage I/II disease should undergo surgical resection followed by adjuvant therapy, while patients with Stage III borderline resectable cancers should undergo neoadjuvant therapy prior to resection. Patients with stage III locally advanced disease should be treated with chemotherapy and/or chemoradiotherapy. Patients with Stage IV and good performance status may receive systemic therapy and those with poor overall health should be given supportive therapy [3].

## Introduction

A meta-analysis of trials performed between 1970 and 2003 demonstrated that 5-FU was superior to best supportive care [4]. But in 1997 a randomized phase III trial demonstrated a survival benefit for gemcitabine over bolus 5-FU with a median survival of 5.65 months as compared to 4.41 months, and 1-year survivals of 18% versus 2%. Gemcitabine had a superior clinical benefit response described as improvement in pain, performance status or weight in 24% of the patients versus 5% in the 5-FU group. Based on this trial, gemcitabine was approved by the Food and Drug Administration for pancreatic cancer and gemcitabine became the standard of care [5]. From then on, a lot of gemcitabine-based combinations have been tested [6]. Gemcitabine plus oxaliplatin or cisplatin showed no statistically significant improvement in survival in phase III trials [7-8]. A phase I/II trial published in 2011 demonstrated exciting results when gemcitabine was combined with nab-paclitaxel as first-line therapy for metastatic pancreatic cancer patients [9]. Gemcitabine has also been tested in combination with several different targeted therapies. A phase III randomized trial demonstrated a statistically significant improvement in overall survival from 5.91 months with single-agent gemcitabine to 6.24 months with gemcitabine plus erlotinib [10]. FOLFIRINOX was initially described in France as oxaliplatin 85 mg/m<sup>2</sup>, leucovorin 400 mg/m<sup>2</sup>, irinotecan 180 mg/m<sup>2</sup>, 5-FU bolus 400 mg/m<sup>2</sup> on day 1 followed by a 46-hour continuous infusion of 5-FU (2400mg/m<sup>2</sup>)

repeated every 2 weeks and has been recommended as an option for first-line therapy in patients with a good performance status [11]. Second-line treatment is not very well established, partially because many of the patients are not strong enough to undergo further treatment. So, gemcitabine is a basement agent for the treatment of pancreatic cancer.

Gemcitabine belongs to one of the nucleoside-derived analog drugs and hENT1 is generally considered to be predominantly involved in gemcitabine transport. Human equilibrative nucleoside transporter protein1 (hENT1, SLC29A1), the first identified member of the human SLC29 family in 1997, [12] is a primary transmembrane protein for the intracellular uptake of the prodrug gemcitabine into tumor cells [13]. Glycosylation is involved in functional property of hENT1 protein and may play key roles in substrate recognition. S-(4-Nitrobenzyl)-6-thioinosine (NBTI, NBMPR) is a small molecule inhibitor of hENT1, it can effectively inhibit the cellular uptake and/or efflux of physiologic nucleosides and many anti-cancer nucleoside analogs, so hENT1 can be divided into NBMPR-sensitive (es) and NBMPR-insensitive (ei). During the decade, the hypothesis that hENT1 overexpression might serve as a predictive biomarker for the efficacy of gemcitabine has been demonstrated by some pre-clinical studies and clinical investigations [14-16]. In a series of 105 patients with pancreatic cancer treated with gemcitabine, higher hENT1 levels were

associated with a significant longer median Overall Survival (OS) (25.69 vs 8.49 months) and median Disease-Free Survival (20.43 vs 9.26 months).

The multivariate analysis confirmed hENT1 expression as an independent factor associated with survival [17]. In RTOG9704, 538 patients were assigned randomly, after surgical resection, to groups that were given either gemcitabine or 5-fluorouracil (5-FU). hENT1 expression was associated with overall and disease-free survival in a univariate and multivariate model in the group given gemcitabine but was not associated with survival in the group given 5-FU [15].

In patients randomly assigned to gemcitabine, 35.2% (126/358) of patients with metastatic pancreatic ductal adenocarcinoma were hENT1 high, there was no difference in survival between the high and low hENT1 subgroups (HR, 1.147; 95% CI, 0.809 to 1.626). This is surprising because previous reports have demonstrated a strong relationship between tumor hENT1 expression and gemcitabine outcome. Up to now, the predictive value of hENT1 in pancreatic cancer therapy is a controversial issue. The relationship between high hENT1 expression and survival in pancreatic cancer samples is in (Table 1) [18-25].

**Table 1:** the relationship between high hENT1 expression and survival in pancreatic cancer samples.

Reference	Total no. of Patients	hENT1 positive rate (%)	Patients	Results
Sinn et al. [19]	88	32	resection	High levels of hENT1 was not associated with improved median DFS
Maréchal et al. [20]	234	39.3	resection	High levels of hENT1 predict longer survival times
Marechal et al. [21]	45	42	resection	High levels of hENT1 have a significantly longer survival
Greenhalf et al. [22]	176	56.3	resection	gemcitabine should not be used for patients with low tumor hENT1 expression
Morinaga et al. [23]	27	59	resection	High levels of hENT1 was significantly associated with a longer survival
Nakagawa et al. [24]	109	71.6	resection	HENT1 is an independent prognostic factor
Farrel et al. [15]	91	80	resection	hENT1 is a molecular and mechanistically relevant predictive marker
Poplin et al. [25]	358	35.2	previously untreated	there was no difference in survival between the high and low hENT1 subgroups

## Conclusion

In conclusion, we found that tumor hENT1 level predicts clinical outcome when undergoing adjuvant gemcitabine-based chemotherapy for resected pancreatic cancer patients. Due to the difficulty of early diagnosis, only 20% of patients with pancreatic cancer are considered surgical resectable, other 80% patients remain to be chemotherapy or radiotherapy or palliative care [26]. The predictive value of hENT1 in previously untreated pancreatic cancer patients still need to be investigated via larger series, preferably within a prospective trial or randomized controlled trial. Low chemosensitivity considerably restricts the therapeutic efficacy of gemcitabine in pancreatic cancer treatment. The process of cellular uptake and intracellular metabolism of gemcitabine in cancer cells is complex, and many factors affect gemcitabine cytotoxicity. Therefore, the combined expression analysis of hENT1 with other markers could contribute to a beneficial clinical outcome.

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