To the Editor,

We had the pleasure of reading the article “Alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH) as candidates for tumor markers in patients with pancreatic cancer” published by Jelski et al in the last issue of the Journal of Gastrointestinal and Liver Diseases, in which the Polish research group describe the potential role of ALDH as a tumor marker for pancreatic carcinoma, along with ADH [1]. As methods, they used serum samples from 165 patients diagnosed with pancreatic cancer and 166 healthy controls. ALDH activity (both class I and II isoenzymes) is then measured by fluorometric methods. Even if this is a very interesting study, worthy of further investigations by prospective studies, its final remarks and correlation are somehow incomplete, as further stated in this Letter to the Editor.

Some members of the ALDH super-family play key roles in the enzymatic detoxification of both endogenous and exogenous aldehydes and in the formation of important metabolic molecules such as retinoic acid or gamma-aminobutyric acid [2]. Thus, mutations in ALDH genes lead to defective metabolism and provide the basic features of diseases such as gamma-hydroxybutyric aciduria, pyridoxine-dependent seizures, Sjögren syndrome or type II hyperprolinaemia [3]. But the most important implication is oncogenesis, as a consequence of impaired retinoic acid synthesis, known to be extremely implicated in stem cell differentiation. Both normal and cancer stem cells share similar characteristics, in that both cell types have the capacity to self-renew and differentiate into multiple cell types [4]. As there is a great need for a universal marker that can identify and isolate these cells, it appears that certain enzymes of the ALDH super-family are able to fulfill this role, being identified in hematopoietic stem cells, melanoma, malignant gliomas and even pancreatic adenocarcinoma, along with other markers such as CD133 [5].

Normal stem cells were shown to contain higher levels of ALDH activity in comparison with their more differentiated progeny, the transit amplifying cells. Confirming this data, Rasheed et al demonstrated that identification of pancreatic cancer stem-like cells is possible through a marker-dependent cell selection and the cells that were proven to possess tumor-initiating properties had a high activity of the intracellular enzyme ALDH, apart from the expression of the cell surface markers CD133, CD44 and CD24 [6]. The main flaw in the study published by Jelski et al is the lack of any correlation between the different pathological subtypes of pancreatic cancer and the cancer stem-like cell phenotype. The authors compare their results with other tumor markers used in the clinic, such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9), but they fail to link the expression of ALDH with the stem-like status, with direct consequence regarding the patients’ clinical prognosis. A high ALDH expression is associated with a worse overall survival in patients that have undergone resection for early stage-disease, according to the report of The Sidney Kimmel Comprehensive Cancer Center in the US.

Thus, an enhanced clonogenic growth of ADLH+ cancer cells is certainly linked as having an important role in the long-term outcome of a patient diagnosed with pancreatic adenocarcinoma by mediating or even stimulating cancer dissemination throughout the abdominal cavity and resistance to chemotherapy with 5-fluorouracil (5-FU) or gemcitabine, according to the European Society for Medical Oncology (ESMO) Practice Guidelines [7]. This statement is valid especially after the initial remission of the disease both clinically and according to all diagnostic procedures, because the cytostatic drug will have eliminated most of the more differentiated cancer cells and both the stem-like pool and the malignant tumor niche will have increased in size, resulting in patient death despite the best supportive care.

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References


Authors’s reply

We read the letter by Tomuleasa et al and first of all we thank them for their interest. Aldehyde dehydrogenase (ALDH) plays an important role in the metabolism of some endo- and exogenous substances (mainly aldehydes). The changes of ALDH activity may be a factor of disorders in metabolic pathways and lead to the development of various diseases and enhance carcinogenesis [1]. In our research we analyzed the activity of ADH and ALDH in the tumor tissue of the digestive system (liver, pancreas, esophagus, stomach, colorectum) cancers [2]. Only in the case of hepatocellular cancer, the activity of ALDH was significantly higher than in healthy liver parenchyma [3]. These results are in agreement with data reported by Tomuleasa et al [4]. In other gastrointestinal cancers, including pancreatic cancer, the activity of ALDH did not show significant differences between cancer and healthy tissues [2]. However, all pancreatic cancer patients were diagnosed with pancreatic ductal adenocarcinoma (G2, pT3) [5]. Also in the serum of patients with pancreatic cancer we observed no increased ALDH activity. Indeed, with increasing tumor stage, the ALDH activity increased, but not such a statistically significant increase was evidenced [6]. Therefore, the discussion did not devote much attention to this fact, focusing on the total activity of ADH and activity of ADH III, comparing them with other tumor markers used in the clinical practice (CA 19-9, CEA).

Rasheed et al examined the prognostic significance and functional features of ALDH expression in pancreatic cancer. The clinical conclusions about it were based on retrospective analyses and were independently validated [7]. The clinical significance of ALDH–expressing cancer stem cells is unclear.

We examined the diagnostic significance of total ALDH activity in the serum of patients with pancreatic cancer. In our present study the diagnostic sensitivity of ALDH activity was 30% and specificity was 34%. In this investigation, ALDH had predictive values for positive and negative results 41% and 38%, respectively and all these values were lower than CA 19-9 and CEA. However, it should be noted that there was a tendency towards increased diagnostic parameters for ALDH in the more advanced stages of the tumors. In patients with advanced stage IV cancer, the sensitivity of ALDH was 42%, specificity 40%, PVPR 50%, PVNR 47%. In our opinion, these results did not indicate that ALDH activity is a very good tumor marker of pancreatic cancer but their potential importance in the diagnosis should not be entirely excluded. There is a need for more extensive studies to verify these results.

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References

Antiviral treatment for HCV-related cirrhosis: Is the effort worth it?

To the Editor,

We read with great interest the study by Bota et al [1] in a recent issue of the Journal of Gastrointestinal and Liver Diseases, where they conducted a thorough review and presented important data regarding the fact that overall SVR rate in HCV-related cirrhotic patients treated with standard of care therapy is 33.3%. SVR was significantly higher in patients with genotypes 2/3 as compared to those with genotypes 1/4 (55.4% versus 21.6%). Even if the SVR rate in HCV cirrhotic patients with genotype 1/4 is very low, with lots of adverse events, it is cost-effective to treat cirrhotic patients with antiviral therapy.

However, we have several questions. Firstly, according to the eligibility criteria, 22 patients with genotype 2/3 in a controlled study [2] should be included in their systematic review. Secondly, Moreno Planas et al did not describe which patients (genotype 1 or 3) achieved SVR and how did one patient without a genotype achieve results in their study. How did Bota and colleagues deal with these data?

Additionally, previous studies of chronic hepatitis C virus treatment have demonstrated variations in response among racial and ethnic groups [3, 4]. In this review, most studies (9/11) were from Europe. Only 94 cases in two other studies were from South Asia and 91 out of 94 patients were genotype 3. Therefore, the study results in this review cannot be extended to patients with HCV-related cirrhosis in East Asia, where HCV genotype 1 is prevalent or in Latin America and Africa.

It is well known that patients of Asian ancestry have a significantly higher probability of viral response than patients of Caucasian and African origin [3, 4]. Furthermore, recent research has demonstrated that the difference has been attributed to a substantially higher frequency of the IL-28B C allele in East Asians [5]. Treatment of patients with compensated cirrhosis has resulted in fewer deaths and hepatocellular carcinomas and transplantations with respect to the no-treatment strategy have been reported [6]. A higher cost-effective method to treat cirrhotic patients in East Asians remains unclear.

A prospective study was carried out to investigate the efficacy and safety of standard interferon with a low accelerating dosage regimen in combination with ribavirin in patients with HCV-related decompensated cirrhosis in our center (unpublished results). SVR rates for genotype 1 and genotype 2 patients were 33.3% (6/18) and 62.5% (5/8), respectively. Regardless of genotype 1 or non-genotype 1, SVR rates were higher compared to the Bota et al study. A higher SVR rate attributed to a substantially higher frequency of the IL-28B C allele in our study needs further clarification.

In conclusion, antiviral therapy using standard of care regimens in HCV cirrhotic patients is possible with a relatively high rate of virological response. Closely monitored, the treatment of patients can last as long as they can tolerate the treatment.

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References

Authors’ reply

Firstly, we want to thank to Dr. Fanpu Ji et al for their interest in our review regarding the response to the standard of care antiviral treatment in patients with HCV liver cirrhosis.

Here are our answers. We did not include in our review the article of Iacobellis et al published in 2007 [1] because the characteristics of the patients included were similar to those of the patients from the article published by the same author in 2009 [2]. The article published in 2009 had a higher number of patients and presumably included also the patients from the paper previously published. We could not obtain an explanation from the author and for this reason we included only the study published in 2009 in the analysis.

Because in the study of Moreno Planas et al [3], which comprised only 12 patients, the results of sustained virologic response (SVR) were not presented separately for the genotype 1 or 3, we included the study in our analysis only for the overall SVR rate, and not for the SVR by genotype.

Unfortunately, information regarding the relationship between IL28B and the SVR in cirrhotic HCV patients was not presented in any of the studies included in the analysis.
Letters to the editor

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References

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