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HIGHLIGHT ARTICLE

BRCA and Pancreatic Cancer: Selection of Chemotherapy

Highlights from the "2012 ASCO Gastrointestinal Cancers Symposium". San Francisco, CA, USA. January 19-21, 2012

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Summary

Germline mutations in BRCA genes are associated with increased risk of pancreatic cancer. There are pre clinical data which suggests that DNA cross linking agents should be used in pancreatic cancer patients with BRCA mutations. This review is an update from the 2012 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium regarding recent developments in the treatment of pancreatic cancer with BRCA mutation. Only one study (Abstracts #217) was presented and it is described here.

Introduction

There are approximately 40,000 new cases of pancreatic adenocarcinoma diagnosed in the USA each year [1]. It is well known that germline mutation in the breast cancer, early onset (*BRCA*) 1 and *BRCA2* tumor suppressor genes are associated with increased risk of ovarian and breast cancer [2]. In pancreatic cancer most of the cases are sporadic but it has been reported that patients with *BRCA2* mutations have 3.5 fold increase risk of developing pancreatic cancer [3]. Past series have found incidence of *BRCA2* mutation as high as 17% in pancreatic cancer patients with strong family history of pancreatic cancer [4]. The association between *BRCA1* and pancreatic cancer is not well defined. However one series from Ashkenazi Jews showed that *BRCA1* and *BRCA2* mutations are observed with nearly equal distribution in pancreas cancer families, suggesting that both genes are associated with pancreatic cancer risk [5].

What Did We Learn at the 2012 American Society of Clinical Oncology (ASCO) GI Cancers Symposium?

Only one of the abstracts at the 2012 GI ASCO symposium dealt with BRCA mutation and pancreatic cancer (Abstract #217 [6]). Retrospective analysis by Tran *et al*. looked at Ontario Pancreatic Cancer Study and pharmacy databases and identified 5 patients with BRCA mutations (4 *BRCA2* and 1 *BRCA1*) who were treated with platinum based regimen. It was a heterogeneous population as 3 patients received platinum based regimen for advanced disease while other 2 patients had resectable and locally advanced disease. Interestingly, patient with locally advanced disease (T4N0) were downstaged after receiving platinum based regimen and eventually underwent resection. The 3 metastatic patients had a very good response to platinum based regimen as well with progression free survival of 12 and 45 months in two of the patients.

Discussion

Patients with BRCA mutations are more susceptible certain drugs such as cisplatin or poly(ADP-ribose) polymerase (PARP) inhibitors.

Pre- clinical data suggest that platinum based regimen maybe effective in BRCA mutations at it exert their cytotoxic effect by binding directly to DNA, causing crosslinking of DNA strands and thereby inducing DNA double strand breaks. However, these damages can not repaired effectively due to lacking functioning *BRCA1* or *BRCA2* [7].

In breast cancer patients there are data to suggest that patients with BRCA mutations are more sensitive to DNA damaging agents such as platinum based regimen [8]. However, interestingly, in ovarian cancer it was found that *BRCA2* mutation was more associated with response to platinum-based therapy when compared with *BRCA1* mutation carriers [9]. In pancreatic cancer, *in vitro* data suggest that pancreatic cancers with *BRCA2* mutations are more susceptible to DNA cross

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Abbreviations PARP: poly(ADP-ribose) polymerase

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liking agents [10]. However, clinically this hypothesis is yet to be validated even though there are cases of patients responding to platinum based regimen after failing multiple lines of therapy [11, 12]. The Abstract #217 presented at the 2012 ASCO GI Cancers Symposium supports the further role of using platinum based regimen in pancreatic cancer with BRCA mutation. Even though the numbers were once again small there was evidence of activity of platinum based regimen in this highly selected subset of population.

PARP inhibitors are class of drugs which can induce cell death in tumors with mutations in certain DNA repair pathways such as the BRCA pathways of double-strand break repair [13]. Similarly to the platinum based regimen, PARP inhibitors were found to have activity in population enriched for *BRCA1* and *BRCA2* mutations [14]. In pancreas cancer, the largest series with BRCA mutations were published from the Memorial Sloan-Kettering Cancer Center, New York, NY, USA [15]. In this series, 15 patients with BRCA mutation pancreatic cancer were identified. Three of those patients received PARP inhibitors while 6 patients received platinum based regimen. The results were promising with median survival of 27.6 months including one patient with complete response which is rare in pancreatic cancer.

Conclusion

The incidence of BRCA mutations in pancreatic cancer is small. However, these subsets of patients are clinically important as they may potentially benefit from "targeted therapy". The abstract presented at 2012 ASCO GI Cancers Symposium supports the hypothesis of using platinum based regimen in pancreatic cancer patients with BRCA mutations. However, the numbers are still very small and further prospective studies are need to be done to validate the potential use of platinum based regimen or PARP inhibitors in pancreatic cancer with BRCA mutations.

Conflict of interest The authors have no potential conflicts of interest

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