Tumori, 98: 364-369, 2012

Association of thymidylate synthase and hypoxia inducible factor-1alpha DNA polymorphisms with pancreatic cancer

Jaime Ruiz-Tovar[1], Maria Encarnación Fernandez-Contreras[2,3], Elena Martín-Perez[4], and Carlos Gamallo[3,5]

[1]Department of Surgery, Hospital Universitario de Elche, Alicante; [2]Department of Gastroenterology, Instituto de Investigación Sanitaria Princesa (IP), Hospital Universitario de La Princesa, Madrid; [3]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHD); [4]Department of Surgery, Hospital Universitario de La Princesa, Madrid; [5]Department of Pathology, Instituto de Investigación Sanitaria Princesa (IP), Hospital Universitario de La Princesa, Madrid, Spain

ABSTRACT

Background. Thymidylate synthase and hypoxia inducible factor-1α play a central role in the control of tumor progression. In the present study, we investigated the effect of three DNA polymorphisms within the thymidylate synthase gene and two within hypoxia inducible factor-1α on the prognosis of pancreatic cancer.

Patients and methods. A retrospective study was performed in 59 patients diagnosed with invasive ductal adenocarcinoma of the pancreas and 159 healthy volunteers. The studied DNA polymorphisms were a variable tandem repeat of 28 bp (rs45445694), a G/C single nucleotide polymorphism (rs34743033), and a deletion of 6 bp (ins1494del 6bp; rs34489327) within the thymidylate synthase gene and C1772T and G1790A single nucleotide polymorphisms within hypoxia inducible factor-1α (rs11549465 and rs11549467, respectively). Variable tandem repeats were determined by specific polymerase chain reaction, whereas thymidylate synthase single nucleotide polymorphism G/C, ins1494del 6pb, and hypoxia inducible factor-1α polymorphisms were identified by polymerase chain reaction and RFLP. Thymidylate synthase and hypoxia inducible factor-1α genotype distributions in patients and healthy volunteers were determined. The impact of the polymorphisms on clinico-pathological variables, including survival, was also studied.

Results. The frequency of carriers of the variant del6bp allele was significantly higher among patients (70.0% *vs* 51.0% of healthy donors, $P = 0.02$); 42% of male patients were homozygous 2R/2R *vs* 13.6% of females ($P = 0.03$), but differences regarding gender were not observed among healthy volunteers. Concerning hypoxia inducible factor-1α C1772T and G1790A single nucleotide polymorphisms, the rates of variant T/T and A/A homozygous genotypes were significantly elevated among patients (18.6% *vs* 5.3%, $P = 0.001$, and 5.1% *vs* none, $P = 0.021$ respectively).

Conclusions. In our study, the variant del14946bp allele within the thymidylate synthase gene, and TT and AA genotypes of C1772T and G1790A hypoxia inducible factor-1α single nucleotide polymorphisms were associated with the development of pancreatic cancer. The 2R/2R genotype of variable tandem repeat thymidylate synthase polymorphism might be a risk factor for pancreatic cancer in males.

Key words: DNA polymorphism, hypoxia-inducible factor-1α, pancreatic cancer, thymidylate synthase.

Correspondence to: Jaime Ruiz-Tovar, MD, PhD, Corazon de Maria, 64, 7° J, 28002 Madrid, Spain.
Tel +34-630534808;
email jruiztovar@gmail.com

Received July 30, 2011;
accepted November 18, 2011.