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MINI REVIEW

Advanced small bowel adenocarcinoma: Molecular characteristics and therapeutic perspectives

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Summary Small bowel cancer represents less than 5% of all gastrointestinal cancers, while small bowel adenocarcinoma (SBA) accounts for about one third of all cancers of the small bowel. Although SBA frequently appears sporadically, some diseases are risk factors, such as Crohn's disease and some genetic predispositions to cancer. Progress in the identification of molecular alterations suggests some similarities in carcinogenesis between SBA and colorectal cancer. Evidence levels for the treatment and prognosis of these tumors are insufficient because of the scarcity of this disease and the absence of randomized trials. Chemotherapy based on fluoropyrimidine plus a platinum salt appears to be the most effective treatment regimen in non-randomized prospective trials for advanced SBA. Targeted therapy, against the angiogenic pathway or the epidermal growth factor receptor (EGFR) pathway, for example, is not yet established, but seems promising given the over-expression of vascular epithelial growth factor (VEGF)-A or EGFR observed in SBA. Phase I and II studies are currently evaluating the safety and efficacy of these targeted therapies in SBA treatment. The low incidence of SBA should promote the development of international collaborations to improve our knowledge of the biological mechanisms underlying these tumors and to set up therapeutic trials.

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Epidemiology

Small bowel tumors represent less than 5% of digestive tumors and correspond mainly to 4 different histological types: adenocarcinoma, neuroendocrine tumors, stromal tumors and lymphomas. Small bowel adenocarcinoma (SBA) accounts for about one third of cancers of the small intestine, the same proportion as observed in neuroendocrine tumors [1]. The incidence of SBA varies according to geographic location, with higher rates in North America and Western Europe, and lower rates in Asian countries. In the United States, the estimated annual incidence of SBA is about 5300 new cases, with 1100 deaths per year. In Europe, the annual incidence of SBA was about 5.7 cases per million inhabitants according to the EUROCARE database between 1995 and 2002, while the annual incidence of colorectal cancer was approximately 420 cases per million inhabitants in the same period [2,3]. In France, an increase in the incidence of SBA was observed in the most recent period, with an estimated rate of new cases of 0.31/100,000 in men and 0.23/100,000 in women over the period 1989—2001 [4].

Men are slightly more likely than women to be affected by SBA (53% of cases), with a mean age at occurrence of around 65 years. The duodenum is the most common tumor site as it is seen in over half of SBA cases, followed by the jejunum and ileum [4]. The increase in the incidence of SBA is mainly explained by the increase in the incidence of the duodenal location. In the preliminary results of the NADEGE cohort study, SBA was located respectively in the duodenum, jejunum-duodenum, jejunum, ileum or indeterminate site in 50.4%, 8.7%, 20.4%, 16.1% and 4.4% of cases [5]. All patients with SBA diagnosed in France from January 2009 to December 2012 have been prospectively enrolled in the NADEGE cohort study (Cohorte nationale d'adénocarcinomes du grêle) whose purpose was to describe the clinical and pathological characteristics, the tumor stage at the diagnosis, the prognosis and the efficacy of the adjuvant and/or palliative chemotherapy [5].

Etiology

Although the cause of SBA is unknown in the vast majority of cases, some bowel diseases and genetic predispositions to cancer have been identified as risk factors. In the NADEGE cohort study, predisposing disease was observed in 65/343 (18.9%) patients [5], including Crohn's disease (8.7%), Lynch syndrome (5.8%), familial adenomatous polyposis (2%), celiac disease (1.7%) and Peutz-Jeghers syndrome (0.5%) [5].

Intestinal diseases

Crohn's disease increases the likelihood of developing SBA, with an estimated relative risk of between 27 and 60 [6]. The risk is correlated with the duration and location of the inflammatory damage. In the nationwide CESAME prospective cohort study, which was mainly designed to assess the risk of lymphoproliferative disorder in patients with inflammatory bowel disease receiving thiopurines, the standardized relative risk compared with the general population was 34 in Crohn's disease affecting the small intestine and 46 for disease duration greater than 8 years [7]. Resections of an inflammatory small intestine segment or long treatment with salicylates seem to reduce the risk of developing SBA. In order to detect synchronous tumors, a complete small bowel exploration needs to be performed with enteroscanner or capsule endoscopy (if there is no small bowel stenosis) before the surgery.

For patients suffering from celiac disease, the risk of SBA is also increased, especially in the case of poor adherence to a gluten-free diet: there is an estimated 30-fold increase in the relative risk compared with the general population [8].

Genetic predisposition

Several genetic predispositions, such as Lynch syndrome, familial adenomatous polyposis and Peutz-Jeghers syndrome, are associated with an increased risk of SBA. The estimated cumulative risk is 5% and 15% for Lynch syndrome and Peutz-Jeghers syndrome, respectively [9,10]. In the NADEGE cohort, the preferred site of SBA in Lynch syndrome was the duodenum or the proximal jejunum (55%), while jejunal and ileal locations were reported in 35% and 5% of cases, respectively [5]. SBA screening is currently not systematically recommended in patients with Lynch syndrome. Given the preferred location of SBA in Lynch syndrome context, the revised guidelines published by the group of European experts suggest inspection of the distal duodenum during upper gastrointestinal endoscopy (if performed) and also of the ileum during colonoscopy [11].

For patients with familial adenomatous polyposis, duodenal adenomas are present in 80% of cases, and degenerate into adenocarcinoma with a cumulative risk of 3—4% by the age of 70 year from the Dutch and Danish polyposis registries [12]. Routine screening for duodenal and ampullary polyps by upper endoscopy with lateral vision is recommended in these patients using the Spigelman score, which takes into account the number, size and histological grade and degree of dysplasia of the polyps, thereby indicating the required rate of endoscopic monitoring.

Environmental factors

Some studies have assessed the impact of environmental factors on the occurrence of SBA. There is no significant correlation between alcohol and tobacco and the risk of SBA [13,14]. Consumption of certain foods, such as red meat, sugar and starchy foods, has been reported to increase the risk of cancer of the small intestine, while the consumption of fiber, fruits, vegetables and fish reduces this risk [15].

Carcinogenesis of the small intestine

Molecular alterations in SBA have been explored only in small series of patients. The main mechanisms of carcinogenicity involved in colorectal cancer have been investigated in SBA.