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Oral cancer in Fanconi anemia: Review of 121 cases

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ABSTRACT

Fanconi anemia (FA) is a rare autosomal recessive genetic disorder characterized by aplastic anemia, progressive pancytopenia, congenital anomalies, and increased risk of cancer development. After hematopoietic stem cell transplant (HSCT), patients have an estimated 500-fold increase in the risk of developing head and neck cancer compared to a non-affected, and the oral cavity is affected in one-third of cases. Thus, this study aimed to better understand the natural history of oral cavity cancer in patients affected by FA. After conducting a keyword search on MEDLINE, we found 121 cases of oral cavity cancer in patients who had been affected by FA. In conclusion, HSCT may increase the risks of oral cancer development, especially after 5 years after the transplant. In the normal population, the tongue is the most affected area. FA patients should be informed of the risks of oral malignant transformation and encouraged to be undergo medical surveillance.

1. Introduction

Fanconi anemia (FA) is a rare autosomal recessive genetic disorder characterized by aplastic anemia, progressive pancytopenia, congenital anomalies such as short stature, hypoplastic thumbs, café-au-lait spots, cardiac and renal anomalies, and increased risk of cancer development (Alter, 2014; Auerbach, 2009).

Despite the fact that hematopoietic stem cell transplantation (HSCT) is the main treatment for bone marrow failure, it increases the risk for solid tumors (Deeg et al., 1996; Curtis et al., 1997). Head and neck cancer risks, for instance, are estimated 500- to 700-fold more likely to develop in HSCT patients than in the normal population. Moreover, oral squamous cell carcinoma (OSCC) is the most common type of cancer developed in such patients (Alter, 2014; Kutler et al., 2003a; Rosenberg et al., 2003). The pathway to cancer development in this population has not been investigated thoroughly, and it remains unclear in the literature. The result of chromosomal instability associated with a defective repair of DNA damage is a possible explanation, since these patients do not have traditional behavioral risk factors such as tobacco and alcohol use (Dong et al., 2015).

In light of the discussion presented, the aim of our literature review is to better understand the natural history of oral cavity cancer in patients affected by Fanconi Anemia (FA).

2. Methodology

2.1. Selection of studies

Firstly, we conducted a keyword search on MEDLINE database using the following terms: *squamous cell cancer Fanconi*; *head neck cancer Fanconi*; *oral malignancies Fanconi*; *oral cancer Fanconi* and *mouth cancer Fanconi*. Inclusion criteria were limited to case reports; case series and clinical research describing patients with oral cancer and Fanconi anemia. Although data on this topic were not limited; we eliminated literature reviews; reports of non-oral sites; patients reported in previous publications; and publications that did not report oral cancer characteristics. Papers written in languages other than the ones understood by the authors were translated into English.

Two people were responsible both for screening the titles and abstracts of the identified studies and for assessing full texts of potentially eligible studies under inclusion and exclusion criteria. Papers that referred to FA cases were read carefully to determine whether oral cancer was mentioned. Discrepancies were solved by team consensus.

2.2. Statistical analysis

Data were analyzed, categorical variables were summarized by frequency (%), and quantitative variables were summarized by median and range. Disease-free survival outcomes were calculated considering

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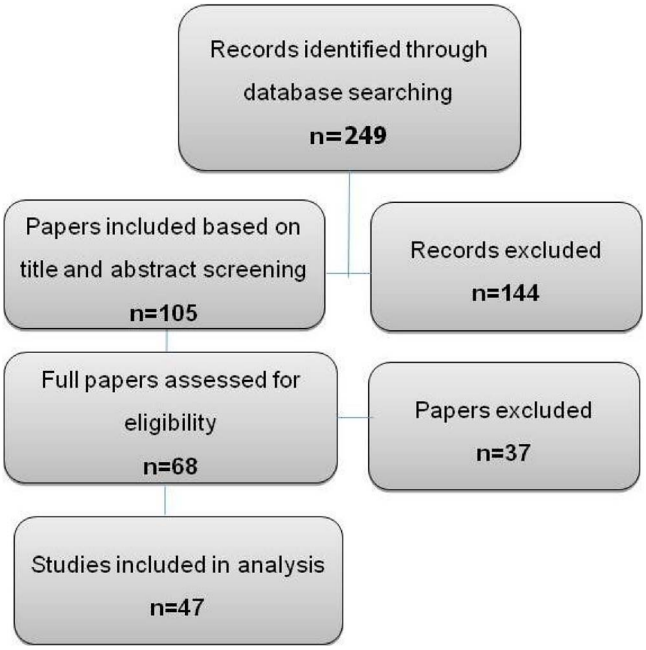

Fig. 1. Study selection process on MEDLINE search.

the age of oral cancer and the time since the patient had undergone HSCT. Kaplan Meier method was used for survival analysis. IBM SPSS software (version 20.0; IBM Corp) was utilized for data analysis, which used Chi square, Pearson and Mann-Whitney tests.

3. Results

3.1. Included records

A total of 249 studies were found in the search. The selection process is shown in Fig. 1. From these, we selected 47 studies published from 1970 to 2016. The characteristics of the studies used are summarized and described in additional supplementary Table S1.

3.2. Patients' characteristics

A total of one hundred twenty-one (121) individuals affected by FA and oral cancer were described in the papers selected. From this number, 69 (57%) were female and 52 (43%) were male, aged from 10 to 52 years old, at a median age of 26.5 years old. Considering the documented information, 56 (46%) cases reported individuals who had undergone HSCT at a median time of 10 years (ranging from 2 to 22); six cases (5%) showed no information about the transplant, and 59 (49%) cases did not go through the transplant procedure. Thirty-four (28%) patients developed more than one primary tumor. From these, 17 cases were detected exclusively in the mouth. Poor correlation was found between age and number of tumors ($p = 0.023$) ***. Older patients presented more cases of tumors. No correlation was found when comparing HSCT and number of tumors. Recurrence was observed in 14 (12%) patients. Four patients developed a third tumor, and all of them were located in the mouth. Regarding the treatment, 41 (34%) patients were treated exclusively due to excision of tumor and the other ones received treatment with radiotherapy and chemotherapy. Table 1 describes the subjects' characteristics and Fig. 2, the time after HSCT of the cases included in this study.

*** Pearson correlation coefficient

Significant statistical differences were observed when age and HSCT were compared ($p > 0.01$). Patients with no HSCT developed OSCC later (31 years) in comparison with transplanted patients (20 years)* (Fig. 3a). More than 75% (n = 42) of the transplanted patients developed OSCC when they were younger than 25 years old, whereas 73% (n = 43) of non-HSCT patients developed oral cancer after their 25 years of age (Fig. 3b).

There was no difference in the incidence of OSSC when gender was considered ($p = 0.088$)**. Notwithstanding, on the one hand, female patients tend to develop cancer when they are older (at age 28) than male patients (at age 23); the median age of cancer incidence in female patients is also higher than in male individuals ($p = 0.011$)*. On the other hand, female patients tend to develop more second primary tumors (31) than male patients (17). Furthermore, when HSCT was compared to second primary tumors, no statistic difference was found*($p = 0.064$).

*T-Test **Mann Whitney Test

3.3. Topography

The tongue was the most affected site as confirmed by 73 cases (60%), followed by gingivae in 11 cases (9%), and by buccal mucosa and retromolar trigone in 7 cases (6%). Only female patients developed lip (n = 5) and mandible (n = 2) cancer. Cancer on the mandible and on the retromolar trigone area was reported only in patients who had not undergone hematopoietic stem cell transplantation. More details are presented in Table 2.

3.4. Survival outcomes

The median of overall survival for patients with oral cancer was 26 years and the median of disease-free survival after transplantation was 10 years. (Fig. 4a and b):

When we compared gender, it was possible to notice that female patients developed cancer later than male patients and it occurred after the transplant. This difference was statistically significant ($p = 0.036$) (Fig. 5a and b):

Finally, the median time of disease-free survival for patients with oral cancer after the HSCT was 21 years and for patients who had not undergone HSCT was 29 years ($p < 0.001$). (Fig. 6.) Around 66% of transplanted individuals presented disease-free survival up to 18 years, while the same happened to 70% of non-transplanted patients.

4. Discussion

Head and neck squamous cell carcinomas (HNSCC) in FA patients were most commonly located in the oral cavity (Kutler et al., 2015). Patients with FA display a marked predisposition for carcinomas of the mucous membranes of the anogenital and oral areas (Kennedy and Hart, 1982). Our study includes 121 cases of OSCC in patients with FA that have been reported on PubMed since 1970.

FA-OSCCs are clinically and genetically similar to sporadic OSCCs, despite having a different etiology (van Zeeburg et al., 2008). While etiology is related to tobacco and alcohol use in the normal population, in FA patients its cause remains unclear. Some authors suggest that the local microbiome (bacteria and viruses) can contribute to oral cancer development; however there is not enough evidence to support this claim (Alter et al., 2013; Furquim et al., 2017; Park et al., 2013).

The first review including oral cancer cases in FA patients described 17 head and neck cancer cases in patients younger than 30 years old, occurring equally in both females and males (Lustig et al., 1995). A review of oral transformation after HSCT that included several hematologic diseases presented a gender distribution of 19:5, in which males had a higher risk of developing secondary oral cancer than females. Yet, males are slightly more likely than females to undergo HSCT (62% to 56%) (Kruse and Grätz, 2009).

Despite the above stated, some authors have indicated a high ratio of squamous cell carcinoma (SCC) occurring more in females than in males (Kennedy and Hart, 1982; Masserot et al., 2008; Reed et al., 1983). On that matter, a prospective study using 754 individuals by the