Critical Reviews in Oncology/Hematology 112 (2017) 136–152

Contents lists available at ScienceDirect

Critical Reviews in Oncology/Hematology

journal homepage: www.elsevier.com/locate/critrevonc

Mucosal melanoma of the head and neck

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http://dx.doi.org/10.1016/j.critrevonc.2017.01.019

ARTICLE INFO

Article history:
Received 6 July 2016
Received in revised form
27 December 2016
Accepted 31 January 2017

Keywords:
Mucosal melanoma
Head and neck
Surgery
Radiotherapy
Targeted therapies
c-KIT immunotherapies
anti PD-1/PD-L1

ABSTRACT

Mucosal melanoma of the head and neck is a very rare and aggressive malignancy with a very poor prognosis. The nasal cavity, paranasal sinuses, and oral cavity are the most common locations.

One-, 3- and 5-year survival rates between 2000 and 2007 were 63%, 30% and 20%, respectively. Cigarette smoking seems to be a risk factor even though the evidence for this is very low. Clinical signs and symptoms are usually nonspecific. While surgery is considered the mainstay of treatment for most mucosal melanomas of the head and neck region, radiotherapy has a role in local control of the disease after surgery. Many new treatment options in the last years, in particular targeted therapies (*i.e.* inhibitors of c-KIT, NRAS/MEK or BRAF) and immunotherapies (anti CTLA-4 and anti PD-1/PD-L1 antibodies), have changed the history of cutaneous melanoma. Despite the different biology, mucosal melanoma is currently treated in the same way as cutaneous melanoma; however, patients with mucosal melanoma were excluded from the majority of recent clinical trials. Recent molecular findings offer new hope for the development of more effective systemic therapy.

1. General information

1.1. Incidence

Malignant mucosal melanomas (MM) are very rare cancers. In 2013, under 850 newly diagnosed cases were estimated to occur in Europe, with an annual incidence rate of 1.5 per million (RARECAREnet, 2017). The most common sites are the head and neck (41%) (Mallone et al., 2012). Incidence is slightly but significantly higher in women than men (1.2 *vs.* 1.0 per million). The disease is unusual in people under the age of 65; in those aged over 65 years, the rate is 6.3 per million. There are geographical differences in the occurrence of MM, with age-adjusted incidence highest in the North (2.2) and lowest in the East of Europe (0.7). During the period 1995–2007, incidence rates remained stable (RARECAREnet, 2017). MM represents 1.3% of all melanomas and they may develop in any mucosal membrane. Conjunctival melanomas (0.5 per million/year) and melanomas in the sinonasal cavity (0.5 per million/year) are the most common, followed by anorectal melanomas (0.4 per million/year) and melanomas in the oral cavity (0.2 per million/year). Anorectal melanoma occurs slightly more often in women, whereas oral melanoma is more frequent in men. (Mikkelsen et al., 2016)

1.2. Survival

MM is an aggressive malignancy with a very poor prognosis. In Europe, according to the RARECAREnet project (RARECAREnet, 2017), in which survival was calculated from 2277 European cases diagnosed between 2000 and 2007, 1-, 3-, and 5-year survival rates were 63%, 30% and 20%, respectively. Five-year survival was 23% in patients aged 25–64 years of age and 19% in patients aged >65 years. In Europe, during the period 1999–2007, 5-year survival remained stable (RARECAREnet, 2017). Despite numerous technological developments in surgery and radiation therapy, as well as advances in systemic modalities, no increased survival advantage has been seen in MM (Lazarev et al., 2014).

1.3. Risk factors

Sun radiation, a major risk factor for cutaneous melanoma, is unlikely to be implicated in MM, which occur on sun-shielded surfaces. For oral MM, cigarette smoking has been suggested as risk factor, because it has been demonstrated that pigmented oral lesions are more prevalent among smokers (Axell and Hedin, 1982). Exposure to formaldehyde has also been suggested to be a risk factor for sinonasal MM, since cases have been reported among workers subject to industrial or professional exposure to this substance (Holmstrom and Lund, 1991). Association with viruses is unlikely, with several studies not showing any link between MM and human papilloma viruses, human herpes viruses, or polyomavirus (Holmstrom and Lund, 1991; Lundberg et al., 2006; Giraud et al., 2008).

2. Pathology and biology

Malignant MM represents a rare group of tumours (0.2%-8% of all malignant melanoma), with different localizations in the body. Head and neck MM comprise less than 1% of all melanomas and the mucosa of nasal cavity, paranasal sinuses and oral cavity are the most common locations.

In contrast to cutaneous melanoma, the biology and pathogenesis of MM of the head and neck region is poorly understood. The latest experimental studies specifically address primary MM of the oral cavity (POMM). Precursors of melanocytes arise from the neural crest, from where they migrate to their final destination through embryonic mesenchyme, along specific pathways (Dupin and Le Douarin, 2003). Most of the melanocytes are located in the epidermis and dermis of the skin, but it is not rare to find them in other body structures such as eyes and mucosal surface of the head and neck region, in particular in the sinonasal region (Patel et al., 2002; Bachar et al., 2008). The presence and the function of melanocytes in the mucosal membrane are not yet clarified, although a few studies have supported the hypothesis of an antimicrobial and immunological function (Mackintosh, 2001; Plonka et al., 2009). Several hypotheses have been put forward on POMM pathogenesis. Early studies supposed that POMM arose from pigmented nevi, pre-existing pigmented areas or de novo from an apparently normal mucosa (Rapini et al., 1985). In 2005, Kahn et al. suggested that POMM could arise from the transformation of a benign oral pigmentation (Kahn et al., 2005).

As for the pathogenesis of other tumour entities, the existence of precursors cells that originate from stem/progenitor melanocytes has also been hypothesized for POMM. These melanocytes, following a series of molecular alterations, would have acquired a malignant phenotype (Bandarchi et al., 2013). Another hypothesis suggested that precursor cells could develop as mature melanocytes remaining in the submucosa. As a result of specific molecular and cytogenetic alterations, they have then acquired a de-differentiated phenotype with the gain of a self-renewal capacity (Cramer, 2009).

The pathogenesis of MM is under the control of several signalling pathways. The analyses of genetic profiling of MM have