Second primary osteosarcoma after retinoblastoma:

A retrospective study

Epidemiology

Retinoblastoma is the most common primary cancer of the eye in children. Retinoblastoma can be hereditary (30-40%), it is usually bilateral and has a positive family history (germline mutations of the retinoblastoma tumour suppressor gene [RB1]): The non-hereditary tumour (60-70%) is characterised by unilateral disease without familiarity (somatic mutations of the RB1 gene) (1,2). Survivors of hereditary retinoblastoma have a higher risk of second malignancies than those affected by non-hereditary disease(3). Soft tissue tumours and osteosarcoma (OS) are the most frequent followed by melanomas and brain tumours (3,4). The median age at OS onset in retinoblastoma survivors is 12 years (6) compared to 15 years in osteosarcoma (OS) unrelated to retinoblastoma(7). Secondary OS is more frequent in the radiation field, with a correlation to dose and age at the time of radiotherapy(5). The latency period between radiotherapy and OS onset is shorter inside than outside the radiation field. No correlation with gender has been described in previously published case reports. The risk of secondary tumours can be higher after alkylating therapy due to a higher risk of mutation of the second RB1 allele (8).

Genetics

RB1 is a negative regulator of the cell cycle and was the first tumour suppressor oncogene described. The relationship between successive loss of function of both alleles of the RB1 gene or partial/complete deletion of human chromosome 13 and a predisposition to develop both retinoblastoma and osteosarcoma has been demonstrated in a number of studies (1,2,9-11). RB1 is implicated in cellular differentiation, cell death, angiogenesis, metastasis and senescence. Campisi *et al* suggested that senescence is rate limiting in cancer development. Inactivation of RB1-mediated senescence mechanisms promotes tumour formation (12). In bone, RB1 regulates the differentiation and senescence of osteoblasts; it is inactivated in 20% to 40% of sporadic osteosarcomas and is linked to poor disease outcome (13). Furthermore, concomitant alterations of the TP53 gene are frequently observed (9,11).

Clinical and treatment outcome

Considering the rarity of osteosarcoma following retinoblastoma, few data are available from retrospective published studies. Almost all osteosarcoma were observed in hereditary retinoblastoma patients and 88% developed the disease after radiotherapy or after a combination of chemotherapy and radiotherapy for retinoblastoma (this data supports the hypothesis that carriers of an RB1 mutation are predisposed to bone

cancer) (3,14). Presentation may be inside or outside the field of irradiation. Osteosarcoma that developed outside the radiation field was mostly in the legs (3). Few cases of secondary metastatic osteosarcoma have been presented in published studies (3,4,14,16). Osteosarcomas that followed retinoblastoma were treated in the same way as primary osteosarcomas (surgery and chemotherapy).

In a retrospective study of eight cases, Lee *et al* showed no significant relation between tumour location (head/neck vs extremities), the extent of surgery (incomplete vs complete), the presence of metastasis at the time of diagnosis or histologic response to preoperative chemotherapy compared with primary osteosarcoma. In the same study, overall survival and event free survival at 2 years were 56.3%±19.9% and 33.3%±18.0%, respectively (15). A local failure occurred in patients with axial tumours who did not undergo complete surgery (16).

Future perspectives

The purpose of this retrospective EMSOS study is to collect information on genetics, the clinical picture, treatment and follow-up that can be used as a basis for future clinical practice management. Secondly, these data might represent an ideal platform to generate a future prospective study in this particular group of patients.

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