COMPARISON OF P53 MUTATIONS IN LOCALIZED AND METASTATIC OSTEOSARCOMA

Introduction. In many cancers, tumors harboring mutations of the p53 gene have a more aggressive clinical course or are more likely to be from advanced disease (1-7). To address the role of p53 mutations in osteosarcoma development and progression we analyzed 247 primary localized osteosarcomas and 25 osteosarcomas that were metastatic at diagnosis. The group included 27 matched biopsy-resection and 21 biopsy-metastasis paired specimens.

Methods. Tumor specimens and corresponding clinical data were obtained from 272 patients with biopsy proven high-grade osteosarcoma of the extremity from six tertiary care institutions. Each subject provided a signed consent form as approved by IRB before study entry. The nature and location of p53 mutations (exons 4 through 10) were examined by PCR-SSCP (single strand conformation polymorphism), confirmed by direct DNA sequencing, and compared with clinicopathologic factors identifiable at the time of diagnosis. The prognostic significance of p53 mutation status was investigated in a cohort of 202 patients with classical osteosarcoma who were treated with chemotherapy and local tumor resection and followed prospectively. Survival analysis of p53 gene status was by the log-rank test and Cox proportional hazards model.

Results. In the entire group of 272 patients, the overall frequency of p53 mutations was 22% (60/272) with 13 of the 60 mutations located in exons 4 or 10. A similar proportion of localized osteosarcomas had alterations of the p53 gene (55/247, 22.3%) compared to tumors from patients with metastases at diagnosis (5/25, 20%; p=0.96). Tumors from patients with localized osteosarcomas and those with metastases at diagnosis also exhibited equal proportions of missense (32/247, 13% vs. 3/25, 12%) and nonsense (23/247, 9% vs. 2/25, 8%) mutations respectively. Patients with p53 missense mutations were older than those with nonsense alterations or a wild-type gene (p=0.01). Tumor site (p=0.006) and tumor size (p=0.002) were the only factors associated with systemic disease status at diagnosis, but neither was related to p53 status.

Examination of paired biopsy-resection and biopsy-metastasis specimens revealed that the p53 status was concordant between the biopsy and later tumor specimens in all cases. In the prospective cohort of 202 patients with localized osteosarcoma, there was no significant association between the presence of a p53 mutation and development of systemic disease recurrence by either univariate (p=0.18) or multivariate (p=0.16) analysis.

Discussion. P53 mutation status was concordant for all paired tumor specimens, and did not differentiate between patients presenting with a localized osteosarcoma and those with metastases at diagnosis. These results indicate that p53 mutations are not late events in osteosarcoma tumor progression as they are evident before the development of metastases. Even for patients presenting with a localized osteosarcoma, p53 status was not a predictor of disease outcome. New molecular prognostic features of osteosarcoma are needed to improve patient stratification and treatment.

References