DC-based Adjuvant Immunotherapy for Patients with Hepatocellular Carcinoma after Primary Treatment

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Dendritic cell (DC)–based immunotherapy has been expected to shed lights on the field of cancer treatments. However, even in the murine model, DC-based immunotherapy has not been as much effective as expected in most solid tumor. We found that the limitation of DC vaccine to solid tumor is likely due to the tumor microenvironments rather than insufficient immune induction. CTL response induced by DC vaccine was quite sufficient and functional for the inhibition of tumor recurrence or metastasis after surgery. Given this information, we have performed clinical studies to evaluate the feasibility, safety and efficacy of DC immunotherapy for patients with hepatocellular carcinoma (HCC). In the prospective phase I/IIa study, 12 HCC patients who had no viable tumor after primary modalities (resection, RFA, PEI and TACE) were included. DC vaccines pulsed with cytoplasmic transduction peptide (CTP)-attached tumor-associated antigens (TAA: AFP, GPC-3 and MAGE-1) were injected subcutaneously near to inguinal lymph nodes. Nine of 12 patients had no tumor recurrence after DC vaccination. Among a total of 144 adverse events (AEs), 129 events (89.6%) were regarded as treatment-emergent AEs, all of which were grade 1 or 2. The majority of patients showed enhanced anti-tumor immune responses after DC vaccination. Recurrence-free patients exhibited relatively stronger anti-tumor immune responses than patients who developed recurrence after DC vaccination, as evidenced by lymphocyte proliferation and IFN-γ ELISPOT assays. The median TTP was 36.6 months in the DC-vaccination group and 11.8 months in the historical control group (hazard ratio, 0.41; 95% confidence interval, 0.18-0.95; *P*=.0031 by log-rank test). In the following multicenter, randomized, open-label phase II trial, 156 patients who achieved complete remission after primary treatments for HCC were included. Patients were randomly assigned to immunotherapy (*n*=77; injection of 3×10^7 DC cells, 6 times over 14 weeks) or control (*n*=79; no treatment). The primary endpoint was recurrence-free survival, and the secondary endpoints were immune response and safety. This phase II study completed recently demonstrated that TAA-pulsed DC vaccine-based adjuvant immunotherapy was well tolerated, and significantly reduced the risk of tumor recurrence in HCC patients after primary physicochemical treatments excluding RFA (HR, 0.49; 95% CI, 0.26–0.94; *P*=0.03). We also found that baseline IL-15 can be a candidate biomarker for DC-based HCC immunotherapy. Details will be presented and discussed in my talk.