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BRIEF REPORT

Remission of Disseminated Cancer After Systemic Oncolytic Virotherapy

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Abstract

MV-NIS is an engineered measles virus that is selectively destructive to myeloma plasma cells and can be monitored by noninvasive radioiodine imaging of NIS gene expression. Two measles-seronegative patients with relapsing drug-refractory myeloma and multiple glucose-avid plasmacytomas were treated by intravenous infusion of 10^{11} $TCID_{50}$ (50% tissue culture infectious dose) infectious units of MV-NIS. Both patients responded to therapy with M protein reduction and resolution of bone marrow plasmacytosis. Further, one patient experienced durable complete remission at all disease sites. Tumor targeting was clearly documented by NIS-mediated radioiodine uptake in virus-infected plasmacytomas. Toxicities resolved within the first week after therapy. Oncolytic viruses offer a promising new modality for the targeted infection and destruction of disseminated cancer.

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Oncolytic viruses (OVs) are promising experimental anticancer agents that, because of their complexity and diversity, can incorporate a variety of novel tumor-targeting and cell-killing mechanisms.[1] Oncolytic viruses have already shown clinical promise as immunotherapeutic agents, driving immune-mediated tumor destruction after intratumoral administration in patients with metastatic melanoma.[2,3] Also, there have been reports of localized tumors responding to an intravenously administered virus.[1] However, the "oncolytic paradigm," whereby a systemically administered OV targets a disseminated cancer and initiates a spreading infection that mediates the cancer's destruction, has not yet been clinically documented.[1]

Multiple myeloma (MM) is a malignancy of terminally differentiated plasma cells that diffusely infiltrate the bone marrow as well as form skeletal and/or soft tissue plasmacytomas (focal lesions). Multiple myeloma typically responds well to alkylator-, corticosteroid-, and immune-modulatory drugs and proteasome inhibitors but eventually becomes refractory to these treatments and is rarely cured.[4] New MM treatment modalities such as oncolytic virotherapy are therefore being actively explored.

MV-NIS is a recombinant oncolytic measles virus (MV) derived from an attenuated Edmonston lineage vaccine strain (MV-Edm) that was adapted to grow on human cancer (HeLa) cells, then engineered to express the human thyroidal sodium iodide symporter (NIS) so that its in vivo spread can be noninvasively monitored by radioiodine single-photon emission computed tomography (SPECT)—computed tomography (CT) imaging.[5] Measles is an enveloped lymphotropic paramyxovirus with a negative-sense RNA genome whose surface glycoproteins not only mediate the entry of the virus into susceptible target cells but also drive the fusion of infected cells with adjacent uninfected cells.[6] Unlike naturally occurring measles, MV-Edm, and hence MV-NIS, targets CD46 as a cell-entry and cell-fusion receptor.[5-7] CD46 is a ubiquitous complement regulatory protein that, fortuitously, is highly expressed on human myeloma cells, making them abnormally susceptible to MV-NIS infection, syncytium formation, and cell killing.[8]

The antimyeloma efficacy of systemic MV-NIS therapy was found to be dose dependent when the virus was administered intravenously in myeloma xenograft models.[7] Antitumor activity was lost in mice that were passively immunized with antimeasles antiserum.[9,10] MV-NIS

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toxicities were not encountered in preclinical dose-finding studies in CD46 transgenic mice and nonhuman primates, even at the maximum feasible intravenous dose.[7] A phase 1 clinical trial was therefore initiated to determine the maximum tolerated dose of intravenously administered MV-NIS in patients with advanced, refractory MM.[11] The trial, which is now almost completed and will be reported in detail elsewhere, has a standard cohorts-of-3 design with a first dose level of 10^6 $TCID_{50}$ (50% tissue culture infectious dose) of MV-NIS, increasing by 10-fold dose increments to a maximum feasible dose of 10^{11} $TCID_{50}$. Eligible patients had relapsing myeloma refractory to approved therapies.

In this current report, we provide preliminary data on 2 patients from the phase 1 trial. These patients were selected for immediate reporting because (1) they were the first 2 patients studied at the highest feasible dose level who were also seronegative for prior measles exposure and (2) they both had no response to multiple rounds of conventional therapy for MM and were therefore at risk for imminent death. Thus, these 2 patients provided a unique opportunity to determine the systemic adverse effects of oncolytic virotherapy in the absence of a preexisting antiviral immune response, as well as the resulting effect on tumor burden. Collectively, these patients provided heretofore unreported insights into the feasibility and risk-to-benefit profile of this novel approach to cancer therapy.

PATIENTS AND METHODS

Selected Study Patients

Patient 1. Patient 1 was a 49-year-old woman with heavily pretreated light chain MM who experienced relapse while receiving no therapy 9 months after her second autologous stem cell transplant (ASCT). Multiple myeloma had been diagnosed 9 years earlier and treated with thalidomide and dexamethasone followed by consolidative ASCT[12]; lenalidomide and dexamethasone[13]; cyclophosphamide, bortezomib, and dexamethasone[14]; and a second ASCT. Immediately before receiving MV-NIS, she had a rapidly enlarging firm, nontender 3-cm-diameter plasmacytoma emanating from the left frontal bone. The serum λ free light chain level had increased substantially from 2.5 to 8.0 mg/dL (to convert to mg/L, multiply by 10) since her previous clinic visit 2 months earlier. Positron emission tomography (PET)—CT revealed multifocal osseous progression of her MM when compared with the previous scan obtained immediately before her second ASCT, with enlargement of the glucose-avid lesion in the left frontal bone and new glucose-avid lesions in the left sternal manubrium, right frontal bone, medial right clavicle, and T11 vertebral body. Bone marrow biopsy, which had yielded completely negative results on day 100 following the ASCT, revealed 3% infiltration with λ light chain—restricted clonal plasma cells.

Patient 2. Patient 2 was a 65-year-old woman with relapsing IgA κ MM refractory to all approved antimyeloma drugs who experienced disease progression while receiving carfilzomib, pomalidomide, and dexamethasone therapy. Her MM had been diagnosed 7 years earlier and had been treated with local radiotherapy; high-dose dexamethasone; lenalidomide and dexamethasone; single-agent bortezomib; cyclophosphamide, bortezomib, and dexamethasone; ASCT; lenalidomide, bendamustine, and dexamethasone; bortezomib, cyclophosphamide, lenalidomide, and dexamethasone; carfilzomib plus dexamethasone; bortezomib, dexamethasone, thalidomide, cisplatin, doxorubicin, cyclophosphamide, and etoposide; and several experimental therapies. Before MV-NIS therapy, she had innumerable palpable (firm, nontender) soft tissue plasmacytomas, especially in the muscles of her lower extremities, ranging in diameter from 2 to 7 cm. Her hemoglobin level was 8.9 g/dL (to convert to g/L, multiply by 10), and her serum κ free light chain value had increased from 6.5 mg/dL to 31.1 mg/dL (to convert to mg/L, multiply by 10) over the previous month. PET-CT revealed numerous fluorodeoxyglucose (FDG)—avid nodules and mass lesions, most prominent below the level of the diaphragm and especially in the soft tissues of the legs. Several of these lesions had increased in size and FDG activity since the previous scan 6 weeks earlier. The largest lesion, located in the left hamstring musculature, measured 74 × 46 mm with a maximum standard uptake value of 8.0. Bone marrow biopsy revealed 1% infiltration with κ light chain—restricted clonal plasma cells.

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