***PROLEUKIN®******Clinical Journal Review:***

**Author(s)**

Steven K. Seung, Brendan D. Curti, Marka Crittenden, Edwin Walker, Todd Coffey, Janet C. Siebert, William Miller, Roxanne Payne, Lyn Glenn,

Alexandru Bageac, Walter J. Urba

**Title**

Phase 1 Study of Stereotactic Body Radiotherapy and Interleukin-2: Tumor and Immunological Responses

**Journal**

Science Translational Medicine, June 6, 2012 Vol. 4 Issue 137

**Study Description**

A single-institution phase 1 study was conducted at the Providence Portland Medical Center. The main eligibility criteria were patients >18 years old; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1; histological confirmation of metastatic melanoma or RCC; at least one metastatic lesion amenable to SBRT in the lung, mediastinum, or liver; and at least one other metastatic site not treated with SBRT.

**Study Duration & Patient Population**

Twelve patients were enrolled from May 18, 2009, through June 28, 2010. They were

assigned to the following cohorts. Cohort 1, a single 20-Gy radiation fraction was administered on the Friday before IL-2; in cohort 2, two 20-Gy fractions were administered on the Wednesday and Friday before IL-2; and in cohort 3, three 20-Gy fractions were administered on the Monday, Wednesday, and Friday before IL-2.

Proleukin® treatment began on the Monday after the last radiation treatment and was administered at 600,000 IU per kilogram by means of intravenous bolus infusion given every 8 hours × 14 planned doses with an additional cycle given after a 16-day hiatus (two cycles = one course of IL-2). Imaging was obtained after each course, and patients with tumor regression could receive up to three courses.

**Study Objective**

This Phase 1 study was designed to assess the safety and tumor responses while exploring the immunological effects of Stereotactic Body Radiation Therapy (SBRT) and IL-2 immunotherapy.

**Background**

Proleukin has been studied extensively in trials combining IL-2 with other biological response modifiers and chemotherapy, but there have been few studies combining radiation and IL-2. This study looks at the effect of combining high-dose per fraction radiation and IL-2.

Investigators at Providence Cancer Center in Portland observed that melanoma or RCC patients who had radiation for urgent palliation in the week before IL-2 had a high systemic response rate. They tested the hypothesis that focal high-dose radiation to a metastatic tumor could be administered safely in conjunction with high-dose IL-2.

Preclinical studies show that exposure of tumor cells to high dose radiation can increase the release of inflammatory cytokines and up-regulate expression of major histocompatibility complex (MHC)

Tumor cells injured by radiation can also release damage-associated molecular patterns

that can trigger a Toll-like receptor 4 (TLR4)–dependent cognate immune response. High-dose per fraction radiation also increases tumor infiltrating activated CD8+ T cells and has been associated with enhanced tumor control at distant sites when combined with immunomodulatory agents in preclinical studies.

**Summary of Results**

* The overall response rate using RECIST criteria was 66%
  + (8 patients responded - 1 CR & 7 PR).

* Six patients with residual radiographic abnormalities on computed tomography (CT) were CRs by positron emission tomography (PET)
* Five of the seven patients with melanoma were PET CRs (71% response rate; 95% confidence interval, 29 to 96%).
* Three of five (60%) patients with RCC had a PR; one patient was a

PET CR.

|  |  |  |
| --- | --- | --- |
|  | CT (%) | PET (%) |
| Complete Response | 1 (8.4) | 6 (50) |
| Partial Response | 7 (58.3) | 2 (16.7) |
| Stable Disease | 1 (8.4) | 1 (8.4) |
| Progressive Disease | 3 (25) | 3 (25) |
| Overall Response Rate | ) 8 (66.7) | 8 (66.7) |
| CR Melanoma | 1 (14.3) | 5 (71.4) |
| PR Melanoma | 4 (57.1) | (0) |
| CR Renal Cell | 0(0) | 1(20) |
| PR Renal Cell | 3 (60) | 2 (40) |

The effectiveness of IL-2 may be enhanced by a change in the tumor microenvironment caused by radiation in melanoma and possibly in RCC

A randomized clinical trial comparing SBRT and IL-2 versus IL-2 alone is under way in melanoma to confirm the response rate and obtain more data about early memory T cell subsets and response.