Effects of Para-Amino Benzoic Acid (PABA), Radiation, and Docetaxel in the 4T1 Breast Carcinoma Murine Model


New York University School of Medicine, Departments of Radiation Oncology and Cell Biology, New York University, New York, NY

BACKGROUND

PABA or p-aminobenzoic acid is a water-soluble compound often used as a component of the Vitamin B-12 complex. It is thought to play a role in the synthesis of purine and pyrimidine bases and amino acid synthesis. It is widely available as a dietary supplement and has been used as a component of sunscreen. We observed a decrease in melanin production in melanoma cells cultured in RPMI, a medium that contains PABA, as compared to DMEM, a medium that lacks PABA. The observation of decreased melanogenesis in these cells along with evidence suggesting radiosensitiveness in melanoma cells with increased pigmentation led to experiments examining PABA in combination with radiation therapy in B16F10 and G361 melanoma cells. PABA and RT significantly inhibited proliferation as compared to radiation alone in both cell lines. To examine whether the enhanced effects of radiation with PABA was dependent on the inhibition of melanogenesis, we studied Lewis Lung (LL) carcinoma cells. Similar results were seen. These findings suggested that the combined effects of PABA and radiation may not depend only on the inhibition of melanogenesis and may apply to other tumor cells.

In-vivo experiments with B16F10 cells in BALB/C mice also demonstrated potentiation of radiation. Further experiments in-vitro and in-vivo revealed enhanced effects of Paclitaxel and Docetaxel when administered in combination with PABA (data not shown).

METHODS

4T1 tumor cells (5 x 10^6) were injected subcutaneously into the flank of BALB/C mice. Three days later, mice were randomly assigned to receive PABA (1 mg/day). For the experiment including docetaxel, a second randomization was performed to docetaxel, 4 mg/kg on days 7, 14, 21, 28, and 35. At 14 days post-implantation, randomization to radiation treatment (RT) was performed. A 60Co source was used to deliver two fractions of 5 Gy to the tumors. Tumors were measured and volumes were calculated weekly using the formula LxW/2. For each group of treated animals, tumor inhibition was reported as the ratio of the average volume compared to that of controls. Results were also compared between groups. P values were determined using Student’s T-test.

RESULTS

4T1 breast murine model RT/PABA/DOCETAXEL

POSSIBLE MECHANISMS

cDNA array analysis was performed on cells cultured in the presence or absence of PABA (100ug/ml). Cdc25A was up regulated and BRCA2 was down regulated in both B16F10 and G361 melanoma cells. This was confirmed at the protein level by Western blot in G361 cells (figureA). PABA may lead to increased cell kill by altering cell cycle checkpoints and decreasing DNA repair (figureB).

Conclusions

- PABA enhances the anti-tumor effect of ionizing radiation in the 4T1 syngeneic murine model
- PABA further enhances the anti-tumor effects of radiation and docetaxel in the 4T1 murine model
- PABA causes alterations in the levels of CDC25A and BRCA2
- Further investigation is needed to determine the mechanism of PABA

References