INTRAVENOUS ASCORBATE AND ONCOLOGIC AGENTS

Updated Data Review and Policies for concurrent use at Anderson Medical Specialty Associates, Southwest College of Naturopathic Medicine Research Institute and Medical Center and Bastyr University Clinical Research Center

Paul S. Anderson
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Abstract:
Intravenous application of ascorbic acid (IVAA) has a long history in adjunctive oncology communities. Its use has stimulated much debate regarding efficacy, safety and appropriate inclusion in oncologic practice. The potential for both antagonistic and synergistic interactions between IVAA and chemotherapies or radiation has existed for some time as an unanswered or confusing question in the naturopathic and allopathic oncology community. The purpose of this publication is to summarize and update the state of understanding of this complicated topic for clinicians employing either standard or integrative oncology care.
INTRAVENTOUS ASCORBATE AND ONCOLOGIC AGENTS

Introduction:

Intravenous ascorbate has been used in oncology practice by naturopathic and alternative allopathic physicians for decades. Published data regarding this therapy shows that it continues to be one of the most commonly employed alternative IV therapies. This popularity has both stimulated awareness of this therapy and concern regarding not only the safety and efficacy of IVAA in the oncology patient but also for the potential of antagonistic reactions with standard therapies.

Publications regarding the postulated mechanisms of action, safety profile, pharmacokinetics and pharmacodynamics were sparse for many years. This led to a highly varied understanding as well as application of IVAA in oncology. In the past five, and especially two, years published data has supported many of the postulated actions of IVC, its pharmacokinetics and dynamics and particularly how those kinetic and dynamic properties can antagonize or synergize the effects of various chemotherapy agents as well as radiation therapies. This data will be presented and summarized.

The goal of this publication is to summarize and update our understanding of the science and practice surrounding this popular and potentially powerful therapeutic agent and how it may interact with standard oncology therapies.

The initial presentation of this basic data was made in February 2013 and the appropriate citation is:


Format:

Agents are grouped by commonly accepted pharmacologic mechanisms. Each group will have footnotes germane to any data currently known regarding ascorbate and that agent. Additionally a grid denoting the reference number and type of response and data set will precede each set of footnotes.

Agents with no currently available published data will have the notation “No direct data” following their name.

Policy:

Agents with positive data, including those with limited negative data combined with multiple positive references, are considered safe to administer in conjunction with ascorbic acid for IV use. Those with no direct data but positive data for other agent class members are considered safe for concurrent use as well. Those with negative data have notations based on published pharmacokinetic data, which outline the specific timing for which intravenous ascorbic acid use is compatible.

Concurrent administration includes administration as close as the same day as the agent mentioned.
CONTENTS:

Agent: Polyfunctional alkylating agents

I. Polyfunctional alkylating agents 8

A. Triazines:

Dacarbazine (DTIC)

Temozolomide (Temodar)

B. Nitrosoureas:

Lomustine (CCNU) 8

Carmustine (BCNU) 9

Streptozocin (STZ, Zanosar)

Semustine (methyl CCNU)

C. Nitrogen mustards:

Mechlorethamine (Mustargen)

Melphalan (Alkeran)

D. Oxazaphosphorines 9

Cyclophosphamide (Cytoxan) 9-10

Ifosphamide (Mitoxana and Ifex) 10

Chlorambucil (Leukeran)

Thiopeta (Thioplex)

Trofosfamide (Ixoten)

E. Alkyl sulfonates:

Busulfan (Mylaran) 10

F. Other Alkylating Drugs 10-11

Procarbazine (Matulane)

Dacarbazine (DTIC)

Altretamine (Hexalen)

II. Platinums

Cisplatin (Platinol) 11

Carboplatin (Paraplatin and Paraplatin-AQ) 12

Oxaliplatin (Eloxatin)
III. Antimetabolites

A. Purine antagonists:
   - Mercaptopurine (6-MP)
   - Thioguanine (6-TG)
   - Fludarabine Phosphate (Fludara, Ofora)
   - Cladribine (Leustatin)
   - Pentostatin (Nipent)

B. Pyrimidine antagonists:
   - Fluorouracil (5-FU)
   - Gemcitabine (Gemzar)
   - Capecitabine (oral pro-S-Fluorouracil)
   - Cytarabine (ARA-C)
   - Azacitidine (Vidaza)

C. Competitive inhibitor of dihydrofolate reductase:
   - Methotrexate (Trexall)

IV. Plant alkaloids

A. Camptothecins:
   - Topotecan (Hycamtin)
   - Irinotecan (Camptosar)

B. Epipodophyllotoxins:
   - Etoposide (VP-16, VePe-sid)
   - Teniposide (Vumon)

C. Non-Epipodophyllotoxins:
   - Amsacrine (Amsidine)
   - Mitoxantrone (Novantrone)

D. Vinca Alkaloids:
   - Vinblastine (Velban)
   - Vincristine (Oncovin)
   - Vinorelbine (Navelbine)
E. Taxanes: 17
  Paclitaxel (Taxol) 17-18
  Docetaxel (Taxotere)

F. Other mitotic inhibitors - Epothilones: 19
  Ixabepilone (Ixempra)
  Estramustine (Emcyt)

V. Polyfunctional Agent
  Arsenic trioxide (Arsenox) 19

VI. Antibiotics
A. Anthracyclines: 20
  Doxorubicin (Adriamycin, Rubex, Doxil)
  Daunorubicin (DaunoXome) 21
  Epirubicin (Ellence)
  Mitoxantrone (Novantrone)
  Idarubicin (Idamycin)

B. Polypeptide:
  Dactinomycin / Actinomycin-D (Cosmegen)

C. DNA Crosslink alkylator:
  Mitomycin (Mutamycin) 21

D. Glycopeptide:
  Bleomycin (Blenoxane)

E. RNA Synthesis inhibitor:
  Plicamycin (Mithramycin)

VII. Hormonal agents
A. Anti-estrogens:
  Tamoxifen (Nolvadex) 22
  Fulvestrant (Faslodex) 23
  Toremifene (Fareston)

B. Aromatase inhibitors:
  Exemestane (Aromasin)
Aminoglutethimide (Cytadren)
Anastrozole (Arimidex) 23
Letrozole (Femara)

C. Progestins:
Megestrol acetate (Megace) 23

D. Anti-androgens: 24
Bicalutamide (Casodex)
Flutamide (Eulexin)
Nilutamide (Nilandron)

E. GnRH / LHRH agonists or analogs:
Leuprolide (Lupron)
Goserelin (Zoladex)

IX. Multi Agent Therapies
A. FOLFIRI
B. FOLFOX 24

IX. Miscellaneous anticancer drugs 25
Hydroxyurea (Hydrea)
Asparaginase (El-spar)
Mitotane (Lysodren)

X. Targeted therapies
A. BCR-ABL tyrosine kinase inhibitor:
Imatinib (Gleevec) 25

B. Inhibitor of cellular signaling by targeting multiple receptor tyrosine kinases; all receptors for (PDGF-Rs) and (VEGFRs):
Sunitinib (Sutent) 26

C. Proteasome inhibitor:
Bortezomib (Velcade) 26

D. VEGF Inhibitors: 27
Bevacizumab (Avastin)
E. Multi target - Inhibitor of VEGFR phosphorylation, glycosylation, mTOR signaling:

Itraconazole (Sporanox, Onmel)  

F. EGFR Inhibitors:  

Tyrosine kinase inhibitors of EGFR.

Erlotinib (Tarceva)  

Gefitinib (Iressa)  

Vandetanib (Caprelesa)  

Lapatinib (Tykerb)  

EGFR competitive receptor binders.

Conatumumab - TRAIL Ligand  

Panitumumab (Vectibix)  

Cetuximab (Erbitux)  

(In development: Zalutumumab, Nimotuzumab, and Matuzumab.)

G. Specific monoclonal antibody therapy:

Rituximab (Rituxan)  

Alemtuzumab (Campath)  

H. mTOR inhibitors:

Temsirolimus (Torisel)  

Everolimus (Afinitor)  

(Ridaforolimus – in development)  

XI. Non-specific immunotherapies and adjuvants:  

BCG  

Interleukin-2 (IL-2)  

Interferon-alfa  

XII. Immunomodulating drugs:

Thalidomide / lenalidomide (Revlimid)  

XIII. Radiation Therapy:  

31-34
Chemotherapy Types:

I. Polyfunctional alkylating agents

A. Triazines:

**Dacarbazine (DTIC)**

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**Temozolomide (Temodar)**

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B. Nitrosoureas:

**Lomustine (CCNU)**

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Carmustine (BCNU)

Potential class synergy with ascorbate suggested in:


Streptozocin (STZ, Zanosar) [No direct data]

Semustine (methyl CCNU) [No direct data]

C. Nitrogen mustards:

Melphalan (Alkeran)

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Mechlorethamine (Mustargen) [No direct data]:

D. Oxazaphosphorines

Cyclophosphamide (Cytoxan)

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<td>2</td>
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Cyclophosphamide (Cytoxan) - continued


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Chlorambucil (Leukeran) [No direct data]:

Thiopeta (Thioplex) [No direct data]:

Trofosfamide (Ixoten) [No direct data]:

E. Alkyl sulfonates:

Busulfan (Myleran) [No direct data]:
F. Other Alkylating Drugs

Procarbazine (Matulane)

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Altretamine (Hexalen) [No direct data]:

II. Platinums

Cisplatin (Platinol)

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Carboplatin (Paraplatin and Paraplatin-AQ)

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<td>1,2,3</td>
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</table>

1. Sullivan, G. et. al. (2011, November). Prospective Randomized Phase I/IIa Pilot Trial to Assess Safety and Benefit Administering High Dose Intravenous Ascorbate in Combination with Chemotherapy in Newly Diagnosed Advanced Stage III or Stage IV Ovarian Cancer. Moderated Abstract [6] presented at the Society for Integrative Oncology, Cleveland, OH.


---------------------------------------------------------------------

Oxaliplatin (Eloxatin) [No direct data]:

---------------------------------------------------------------------
III. Antimetabolites

A. Purine antagonists:

Mercaptopurine (6-MP) [No direct data]:

Thioguanine (6-TG) [No direct data]:

Fludarabine Phosphate (Fludara, Oforta) [No direct data]:

Cladribine (Leustatin) [No direct data]:

Pentostatin (Nipent) [No direct data]:

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B. Pyrimidine antagonists:

Fluorouracil (5-FU)

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<td>1,2,3,4</td>
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Gemcitabine (Gemzar)

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<td>1,2,3,4,5</td>
<td>5,6,7</td>
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C. Competitive inhibitor of dihydrofolate reductase:

Methotrexate (Trexall)

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IV. Plant alkaloids

A. Camptothecins:

Topotecan (Hycamtin) [No direct data]:

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Irinotecan (Camptosar)

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B. Epipodophyllotoxins:

**Etoposide (VP-16, VePe-sid)**

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**Teniposide (Vumon) [No direct data]:**

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C. Non-Epipodophyllotoxins:

**Amsacrine (Amsidine) [No direct data]:**

**Mitoxantrone (Novantrone) [No direct data]:**

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D. Vinca Alkaloids:

**Vinblastine (Velban)**

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Vincristine (Oncovin)

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<td>Positive Response</td>
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Vinorelbine (Navelbine) [No direct data]:

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E. Taxanes:

Paclitaxel (Taxol)

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Paclitaxel (Taxol) - continued


7. Sullivan, G. et. al. (2011, November). Prospective Randomized Phase I/IIa Pilot Trial to Assess Safety and Benefit Administering High Dose Intravenous Ascorbate in Combination with Chemotherapy in Newly Diagnosed Advanced Stage III or Stage IV Ovarian Cancer. Moderated Abstract [6] presented at the Society for Integrative Oncology, Cleveland, OH.

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Docetaxel (Taxotere)

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F. Other mitotic inhibitors - Epothilones:

Ixabepilone (Ixempra) [No direct data]:

Estramustine (Emcyt) [No direct data]:

V. Polyfunctional Agent

Arsenic trioxide (Arsenox)

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<td>Positive Response</td>
<td>2, 3, 5</td>
<td>6</td>
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6. Arsenic trioxide induced apoptosis was not enhanced by ascorbic acid in normal cells, suggesting that this combination may be selectively toxic to some malignant cells – Dai, J.; Weinberg, R. S.; Waxman, S.; Jing, Y. (January 1999). "Malignant cells can be sensitized to undergo growth inhibition and apoptosis by arsenic trioxide through modulation of the glutathione redox system". Blood 93 (1): 268–277. PMID 9864170. http://bloodjournal.hematologylibrary.org/cgi/content/abstract/93/1/268.

-----------------------------------------------------------------------------------------------------------------
VI. Antibiotics

A. Anthracyclines:

Doxorubicin (Adriamycin, Rubex, Doxil)

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Daunorubicin (DaunoXome) and Epirubicin (Ellence)

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Mitoxantrone (Novantrone) [No direct data]:

Idarubicin (Idamycin) [No direct data]:

B. Polypeptide:

Dactinomycin / Actinomycin-D (Cosmegen) [No direct data]:

C. DNA Crosslink alkylator:

Mitomycin (Mutamycin)

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D. Glycopeptide:

Bleomycin (Blenoxane)

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E. RNA Synthesis inhibitor:

Plicamycin (Mithramycin) [No direct data]:

VII. Hormonal agents

A. Anti-estrogens:

Tamoxifen (Nolvadex)

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Fulvestrant (Faslodex) [No direct data]:

Toremifene (Fareston) [No direct data]:

B. Aromatase inhibitors:

Exemestane (Aromasin)

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[At most upon coadministration of HDIVC with daily po drug there would be a 6-12 hour window of possible inhibition.] 2013 Datapharm Communications Ltd.http://www.medicines.org.uk/emc/medicine/2484/SPC

Aminoglutethimide (Cytadren) [No direct data]:

Anastrozole (Arimidex) [No direct data]:

Letrozole (Femara) [No direct data]:

C. Progestins:

Megestrol acetate (Megace) [No direct data]:
D. Anti-androgens:

Bicalutamide (Casodex) **[No direct data]**:

Flutamide (Eulexin) **[No direct data]**:

Nilutamide (Nilandron) **[No direct data]**:

E. GnRH / LHRH agonists or analogs:

Leuprolide (Lupron) **[No direct data]**:

Goserelin (Zoladex) **[No direct data]**:

IIX. Multi Agent Therapies

A. ASC and FOLFIRI

FOL= Leucovorin Calcium (Folinic Acid), F= Fluorouracil, IRI= Irinotecan Hydrochloride

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B. ASC and FOLFOX

FOL= Folinic acid (leucovorin)  F = Fluorouracil (5-FU)  OX = Oxaliplatin (Eloxatin)

As Ascorbate is not detrimental to the efficacy of FOLFIRI [1] and the major change in therapy between FOLFIRI and FOLFOX is a Platin (instead of a tecan), and as ascorbate appears synergistic with Platins [2] it would be reasonable to assume that Ascorbate would only improve efficacy of FOLFOX or FOLFIRI.

IX. Miscellaneous anticancer drugs

Hydroxyurea (Hydrea)

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X. Targeted therapies

A. BCR-ABL tyrosine kinase inhibitor:

Imatinib (Gleevec) – Positive in vitro

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B. Inhibitor of cellular signaling by targeting multiple receptor tyrosine kinases; all receptors for (PDGF-Rs) and (VEGFRs):

Sunitinib (Sutent) [No direct data]:

C. Proteasome inhibitor:

- Bortezomib (Velcade)

Concern: Potential inhibition in vitro by ascorbate [1]

IVC Administration Note:

Given the pharmacokinetics of (Maximum proteasome inhibition occurs within 1 hour, and most effective inhibition wanes throughout the 12-24 hours following administration[2]) and IV Ascorbate we (BORC and AMSA Tx guidelines) recommend IVC as appropriate the day prior to, or 24 - 48 hours following bortezomib dosing.

Oral ascorbate?

Conclusions: No antagonism of bortezomib is seen in preclinical in vivo experiments, where EGCG or ascorbic acid plasma concentrations are commensurate with dietary or supplemental intake. The data suggest that patients receiving bortezomib treatment do not need to avoid normal dietary consumption of green tea, vitamin C-containing foods, or EGCG or vitamin C dietary supplements. [3]


D. VEGF Inhibitors:

Bevacizumab (Avastin)

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E. Multi target - Inhibitor of VEGFR phosphorylation, glycosylation, mTOR signaling:

Itraconazole (Sporanox, Onmel) [No direct data]:

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F. EGFR Inhibitors:

Tyrosine kinase inhibitors of EGFR.

Erlotinib (Tarceva)

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Gefitinib (Iressa) [No direct data]:

Vandetanib (Caprelesa) [No direct data]:

Lapatinib (Tykerb) [No direct data]:

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EGFR competitive receptor binders.

Conatumumab - TRAIL Ligand

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Negative in vitro study with cells preloaded with ASC:


Panitumumab (Vectibix) [No direct data]:

Cetuximab (Erbitux) [No direct data]:

(In development: Zalutumumab, Nimotuzumab, and Matuzumab.) [No direct data]:

G. Specific monoclonal antibody therapy:

Rituximab (Rituxan) [No direct data]:

Alemtuzumab (Campath) [No direct data]:

H. mTOR inhibitors:

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Everolimus (Afinitor) [No direct data]:

(Ridaforolimus – in development) [No direct data]:

XI. Non-specific immunotherapies and adjuvants:

BCG [No direct data]:

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Interleukin-2 (Aldesleukin)

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IVC Lowers IL-2 levels [1] – Use apart from IL-2 Tx t1/2 is roughly 7 minutes [2] and clearance is practically complete at 45 minutes.


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Interferon-alpha

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Positive in vitro study:

XII. Immunomodulating drugs:

**Thalidomide / lenalidomide (Revlimid)**

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Positive basic science:


XIII. Radiation Therapy:

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<tr>
<td>Positive Response</td>
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<td>4,5,6,7,8,9,11</td>
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1. In Vitro Positive pre / co-treatment with ascorbate+Vit K(3)

   - “In addition, cell death caused by VC+VK(3) treatment as well as by prolonged VC treatment is consistent with cell demise by autoschizis, not apoptosis. This report confirms and complements previous observations about this new mode of tumor cell death. It supports the contention that a combination of VC+VK(3), also named Apatone, could be co-administered as a nontoxic adjuvant with radiation and/or chemotherapies to kill bladder tumor cells and other cancer cells without any supplementary risk or side effects for patients.”


2. In Vitro positive:


3. In Vitro positive:

   - “In conclusion, pharmacological concentrations of ascorbate radiosensitize GBM primary cells to a much greater extent than astrocytes; this large therapeutic ratio may be of clinical significance in radiation-resistant cancers.”


4. Positive ASC and K3 in vivo:


5. Radiation was targeted better toward cancer cells and less toward normal cells in one mouse study


6. A randomized human trial of 50 patients evaluated the effect of combined Vitamin C 5gms/day and radiotherapy in different tumor types and noted more complete responses to radiation in the vitamin C group

7. Murine fibrosarcoma mouse model showing increased radiation efficacy in ascorbate pre-treated animals. “The data suggest that after high-dose ascorbic acid the radiation dose given to cancer patients could be increased without increasing acute complications but with an expected increase in tumor-control probability.” “Although a single dose of ascorbic acid delivered at a dose of 4.5 g/kg body wt ip (50 min before irradiation) significantly increased the radiation tolerance of both skin and bone marrow, tumors were not protected.” [Human equivalent doses would be 35 to 325 grams of ascorbate].


9. Ascorbate and radiotherapy outcomes in head and neck cancer: The results of the present study indicate that the patients having better response to the treatment (All the patients received chemoradiotherapy in the form of concurrent cisplatin (35mg/m2 weekly) and radiation to a total dose of 7,000 cGy by a Cobalt-60 machine, daily single dose comprising of 200 cGy, five days a week regimen over a period of seven weeks.) had higher plasma levels of ascorbic acid, while the patients showing partial or no response had lower levels of ascorbic acid.


10. This study was conducted to examine the utility of the combined use of ascorbic acid (AsA) and radiation in clinical applications. We investigated cell survival, DNA fragmentation, and caspase activation after X-ray irradiation and AsA treatment of human leukemia HL60 cells. The number of living cells decreased after combined X-ray irradiation and AsA treatment (2 Gy + 5 mM) in comparison with that after X-ray irradiation (2 Gy) or AsA treatment (5 mM) alone. DNA fragmentation was more in the cells subjected to combined X-ray irradiation and AsA treatment than in those subjected to X-ray irradiation alone. Caspase-3, caspase-8, and caspase-9 were highly activated following combined X-ray irradiation and AsA treatment, but caspase-8 activity was not markedly increased after X-ray irradiation alone. Bax levels in the mitochondrial membrane fractions were increased after AsA treatment alone and after combined X-ray irradiation and AsA treatment. However, there was no apparent increase in the Bax levels after X-ray irradiation treatment alone. Thus, this study confirmed that supplementing X-ray irradiation with AsA treatment results in increased apoptosis in HL60 cells. With regard to the apoptosis-inducing factors, we hypothesized that Bax and caspase-8 were activated after combined X-ray irradiation and AsA treatment compared with either treatment alone.

11. Conclusions:

- GBM cells are sensitive to ascorbate in clinically achievable concentrations
- Ascorbate toxicity is mediated through the production of hydrogen peroxide and is at least in part dependent upon the presence of metals
- Ascorbate sensitizes GBM cell lines to ionizing radiation
- Ascorbate sensitizes GBM xenografts to ionizing radiation and temozolomide.
  - Allen BG et.al. High-dose ascorbate enhances chemo-radio-sensitization in GBM. Poster Presentation, American Society for Radiation Oncology 2012