Overcoming Chemotherapy Resistance

Breaking Through the Barriers

2008 Followup and Additional Information

Mechanisms of Chemotherapy Resistance

- A: cancer cells mutate and the resistant populations flourish ("survival of the fittest").
- B: gene amplification: hundreds of copies of genes which produce chemo-inactivating proteins (inc. MDR gene expression).
- C: P-glycoprotein pump which pumps drug out of cells (inc. MDR expression).
- D: cancer cells inactivate the pump which brings the drugs into the cells (e.g. decreased expression folate transporter with MTX).
- E: cancer cells "learn" to repair DNA damage caused by some chemo drugs (inc. nucleoside excision repair with alkylating agents and platinum drugs; inc. O alkyl-guanine alkyl transferase with nitrosureas, procarbazine, and temozolamide).
- F: cancer cells "learn" to inactivate chemo drugs or decrease their activation (decreased folypolyglutamyl synthetase with MTX or decreased deoxycytidine kinase with cytosine arabinoside, fludarabine phosphate, and cladrabine).
- G: increased detoxification (increased glutathione or GSH tranferase)

Supplements Which Can Help Overcome Chemo-Resistance

- It's a misconception that antioxidants and other supplements are contraindicated with chemo or radiation - most studies actually show a benefit (recent revue by Davis Lamson ND showed 24 of 27 studies demonstrated improved outcomes with supplements used alongside chemo. The most recent review by Keith Block, MD, Canc Treatment Rev, March 14th, 2007, found "increased survival times, increased tumor responses and fewer toxicities").
- Supplements can:
  - Improve delivery of chemo to tumors (gingko and niacinimide)
  - Keep the chemo inside cells (theanine, EGCG, glutamine with MTX)
  - Push the cancer cell into a more susceptible state (arginine and quercetin)
  - Prevent deactivation of chemo by the cancer cell (theanine and quercetin)

Supplements, cont'd

- Prevent cancer cells from repairing themselves (caffeine)
- Force apoptosis (curcumin)
- Support immune system
  - Theanine (increases interferon gamma)
  - Arginine (increases NKC and T-cell function)
  - American ginseng (increases T-cell function)
  - Melatonin (increases IL-2, epidermal growth factor)
  - Avemar (increases T-cell function)
  - Vitamin C and others
  - AHCC - triples natural killer cell activity
- Prevent Metastases - (modified citrus pectin)

Vitamin C Plus K3

- Vitamin C alone has been found to have cytotoxic effects against most cancer cell lines in vitro (Dr. Mark Levine, NIH division of Diabetes and Kidney diseases). These in vitro concentrations are easily achievable in vivo with IV C. The mechanism appears to be intracellular accumulation of H2O2.
- Vit C has also been found to potentiate the effects of chemo (Zaizen, et al., J cancer Res Lin Oncol, 1986; Prasad, et al, Pol J Pharmacol and Pharm, 1992; Koch and Biaglow, J Cell Physiol, 1978) and radiation therapy (Hanck, Prog Clin Biol Res, 1988).

Vitamin C Plus K3 Cont'd

- Vitamin K3 alone has demonstrated anti-tumor activity against multiple rodent and human cancer cell lines.
- Synergism noted with doxorubicin, 5 FU, vinblastine, vincristine, mitomycin, bleomycin, cisplatin, mitoxanthrone, MTX, and many others.
- Phase I trials in humans 400-500 mg/day showed no toxicity in combination with mitomycin. Phase II trials of IV K3 (2.5 gms/m2) with mitomycin showed objective response but 30% showed hemolysis (Gold, Cancer Treat Rep, 1986)

Vit C Plus K3 Cont'd

- Vit C and K3 combination showed synergistic activity in a 100/1 ratio in breast, endometrial and oral epidermoid carcinoma cell lines in concentrations 10-50 times lower than for the individual vitamins (Noto, et al, Cancer, 1989).
- Co administration of C plus K3 with adriamycin, bleomycin, mitomycin C, vincristine or cisplatin increased growth inhibitory effect by 3-14 fold (Buc Calderone, et al., Curr. Med. Chem. 2002).

Vitamin C Plus K3, cont'd

- Other studies show similar synergistic effects (Verrax, et al, Eur J Med Chem 2003; Taper, et al., Life Sci 2004; Taper, et al, Anticancer Res, 1996).
- Several clinical trials in prostate cancer reveal significant benefit with potentiation of chemotherapy Dewez, et al, Eur J Clin Biochem, 1993.

Vit C and K3 Mechanism of Action

- High levels act via oxidative stress and are cytotoxic via necrosis or autoschizis.
- Low levels kill by a non-oxidative mechanism involving transcription factors to produce autochizis and apoptosis.

Vit C and K3 in Urothelial Tumors

- Wassim Kassouf, et al, J Urol, 2006 showed significant antitumor activity of C plus K3 in vitro and in vivo in mice.
- Same paper showed significant potentiation of gemcitibine against bladder cancer in vivo

Using IPT's Capabilities to Overcome Resistance

- IPT uses low doses of chemo therefore unique combinations of drugs can be used with less toxicity.
- Fractionated low doses allow twice weekly sessions with the ability to alternate protocols to delay and possibly eliminate resistance.
- Insulin itself has the capability of helping to overcome chemo resistance (Uruguay study).

Case Presentations and Followup of Previous Cases

- Case I: K.M. 62 y.o. woman dx'd in 2004 with poorly differentiated ductal carcinoma. Lumpectomy. Showed ER+, PR-, HER2+
- Refused chemo at time of dx.
- 1/25/07 PET scan showed L chest wall involved, + supraclavicular and axillary nodes and large (8 cm) mass in L breast;
- dx: "Stage IV"
- Patient had no treatment until arriving at our office in July, 07
- On initial exam, she was found to have a mass essentially having replaced her L. breast, extensive involvement of the skin of the breast and entire left chest wall, large axillary nodes and extensive lymphedema of the left arm. She had severe pain over the entire L. chest. Dx.: "inflammatory breast cancer".

Case I cont'd

- Ca 27-29 on that day was 4454.87.
- Pt. was started on a Adriamycin/Taxotere regimen 2X/wk.
- Pt. was also given IV vit C 2X/wk., chelation weekly
- Many supplements were used including Epicore, Aprastar, vit D3 30,000 IU's IM/week
- Pt. used a low glycemic, all organic diet.
- Colonics were done 1/wk, also lymphatic drainage.

Case I, cont'd

- Initially, patient's condition seemed to deteriorate. Her skin lesions worsened and spread (Typical appearance of "inflammatory breast cancer")
- Ca 27-29 levels rose over the next month to over 8200! Albumin levels drop to 2.2, with alk phos 510, and elevated liver enzymes and massive systemic edema begins.
- We then institute a 2X/wk alternating regimen of 5FU, leucovoran and mitoxanthrone, alternating with CAMF.
- We also add IV albumin 37.5 gms., 1-2X/wk. to help with the edema.
- Over the next month, patient's Ca 27-29 drops into 2000 range. Despite a reduction to once weekly IPT (still alternating regimen), the Ca 27-29 drops to 329 as of 10/17/07.

Case I, cont’d

- Pt’s skin lesions are entirely cleared.
- Left breast has returned to a normal, soft feel.
- Systemic edema has almost completely cleared and liver functions gradually improving.
- Pt. has begun to travel and has almost returned to a normal life.

2008 Followup of Case I

- Pt survived until June 2008 when she began to complain of abdominal pain. She was scanned and multiple gallstones were seen on ultrasound. However, at laparoscopy, multiple metastatic intra-abdominal tumors were found and the patient rapidly declined and passed away in peace, surrounded by her family.

Case II

- B.J.: 61 yo. Stage IV Breast Ca with mets to bone.
- April ‘04, MD noticed lump in L. breast, recommended mammogram. Lumpectomies done X4 due to poor margins. Sentinel node +, ER+,PR+, HER2-.
- Pt. refused chemo, radiation and Arimidex.
- Nov. ‘06 bone scan WNL.
- April ‘07, after pain complaints, PET showed lung mets, paratracheal nodes, R kidney and multiple lesions in spine, bilateral ileac crests, ischia, acetabula, sacrum and proximal R femur.
- 6/12/07 bx. R ileum showed metastatic adeno ca.

Case II cont'd

- Ca 27-29 was 339 several months before admission.
- On admission, Ca 27-29 1023, Ca125 >1400.
- She was started on alternating IPT regimen 2X/wk CAMF alternating with 5 FU, leukovoran and mitoxanthrone.
- Originally no oral supplements because she was followed by a kinesiologist who tested everything we proposed as negative (although she tested OK when we did it).
- Added Zometa 9/23/07 (1/2 dose at first then 3/4 dose- no adverse reaction).
- Ca 27-29 470 on 10/10/07 and Ca125 415.
- Pt's bone pain is gone and functioning has improved despite her resistance to change in diet and taking supplements.

2008 Followup of Case II

- B.J. is still “alive and kicking” impressing our entire staff with her courage and grace!

Case III

- W.L. 78 yo pt. with NSCLC (squamous cell) .
- Jan-Feb ‘07 patient felt fatigued and began losing weight and suffered episodes of bronchitis X 2. He went to an internist who recommended CXR - RLL lesion. Bx: squamous cell carcinoma. PET: primary lesion plus bilat hilar spread and pleural spread.

Case III cont'd

- Pt had been pack and 1/2 per day smoker until 9 yrs PTA.
- Initial CEA was 3.9 but Ca 27-29 was 83.41 and Ca 125 was 37.5.(nl <35)
- Pt begun on Cisplatin/etoposide regimen 2X/wk plus IV vit C 2X/wk. This cont'd 5 wks w/o apparent benefit. Pt c/o increasing dyspnea.
- Pt switched to gemcitibine/cisplatin alt. with gemcitibine/vinorelbine once weekly each.
- Pt's dyspnea rapidly cleared and Ca 27-29 reduced to 72 and Ca 125 reduced to 21.
- PET 8/30/07 showed less metabolic activity in primary lesion and complete disappearance of hilar and pleural activity

2008 Followup of Case III

- W. L. completed his treatment and did well with no cancer recurrence until he died of a sudden M.I. in May 2008

New 2008 Cases

- Further experience with alternating chemotherapy regimens in the IPT setting, using vitamin C, vitamin K3, intensive supplementation and lifestyle modification

2008 Case I

- R.C is a 59 y.o. woman who presented with breast cancer of the right breast (2.7 cm by 3.3 cm by 2.8 cm lesion plus a 8 x 7 mm 2nd lesion) metastatic to the right axilla.
- She'd had yearly mammograms which were considered "normal" until Nov., 07 when she had an abnormal mammogram followed by confirmatory sonogram and MRI.

2008 Case I cont'd

- Biopsy of the larger lesion revealed invasive ductal carcinoma. Biopsy of the axillary node confirmed metastatic breast cancer.
- PET scan in Dec., 07 revealed extremely avid lesions in the above areas (average SUV 21.9).

2008 Case I cont'd

- On 1/23/2008, pt. began an alternating twice weekly IPT using Cyclophosphamide, 5FU and mitoxanthrone, alternating with cyclophosphamide, 5 FU and methotrexate.
- She also did twice weekly I.V. vitamin C infusions with vitamin K3 in a 100/1 ratio.
- Multiple supplements and lifestyle changes initiated.

2008 Case I cont'd

- Pt had followup diagnostic studies in 2/08 (MRI), 4/08 (sonogram) and 7/08 (PET). Each scan showed progressive improvement with shrinking lesions and no abnormal activity on the PET.
- On April 7th, 2008, patient underwent lumpectomies for the two tiny remaining lesions and 4 axillary nodes were removed.

2008 Case I cont'd

- Pathology reports of the breast lesions and all four nodes were negative for cancer.
- As mentioned, followup PET scan post op in July, 2008, entirely WNL.

2008 Case II

- L.K is a 51 y.o. woman, an RN, who presented with a history of metastatic sarcoma with severe abdominal pain and vaginal bleeding.
- Prior MRI (Dec. 07) showed numerous lung metastases, a pelvic mass 9.5 x 8.2 cm "markedly increased" from prior scan 5 mos previously, and severe hydronephrosis of the left kidney and moderate hydronephrosis on the right.

2008 Case II cont'd

- On initial exam the patient was seen to have a large fungating mass, protruding through the vagina. This mass was bleeding intermittently
- The patient was started on twice weekly IPT on 1/13/08, using etoposide, mesna and iphosfamide alternating with doxorubicin, mesna and iphosfamide.

2008 Case II cont'd

- On 4/16, after consulting the German "Biofocus" test, dacarbazine was added to the second protocol. On 5/1, paclitaxel was substituted for etoposide in protocol 1 and cisplatin substituted for doxorubicin in protocol 2.
- Clinically, the initially visible lesion shrank significantly and was no longer visible externally

2008 Case II cont'd

- Pt's pain was relieved significantly as was her need for pain medication.
- She completed treatment in June, 2008 and returned to her home out of state.
- We spoke to her in August and she was essentially pain free.

2008 Case III

- N.L. is a 45 y. o. woman who presented with stage III/?IV breast cancer. Initial staging PET/CT showed 2 hypermetabolic lesions in the left breast with multiple hypermetobolic nodes in internal mammary chain and anterior to the heart, and a hyperbolic mass in the left adnexa.

2008 Case III cont'd

- On 7/10/08, IPT was begun on a twice weekly alternating protocol: cyclophosphamide, epirubicin, 5 FU alternating with cyclophosphamide, methotrexate, 5 FU, vincristine.
- Her only abnormal baseline tumor marker was a CA 125 of 48.5 (interesting in view of the adnexal mass). By week 4, that marker was 12.8.

2008 Case III cont'd

- MRI on 8/18/2008, showed "considerable decrease in size in both breast lesions since prior study of 5/30/2008". This was confirmed on physical exam of the breast.
- PET/CT 8/27/08 showed much less metabolic activity (SUV 2.9) and disappearance of the smaller breast lesion. All hypermetabolic activity of nodes were completely resolved. The left adnexal mass was undetectable.
- Treatment is being tapered.

Summary

- Alternating regimen is well tolerated and appears to be effective.
- Although one could ascribe the improvement merely to sensitivity to the newer drugs, the especially rapid and profound response in poor prognosis patients suggests the alternating regimen is especially effective.
- Plan is to use an alternating regimen as initial treatment and observe results. Will report next IPT conference (today's case studies).
- Next year we plan to report results of using circulating tumor cell analysis to choose chemotherapy regimen.