PILOT STUDIES PROVING EFFICACY OF DENDRITIC CELL THERAPY TO PREVENT RELAPSES IN PATIENTS OF OVARIAN CA

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BACKGROUND

- DEADLIEST MALIGNANCY
- AFFECTS FEMALES OF ALL AGE GROUPS
- REGULAR RELAPSES
- MORTALITY IS UPTO 85%
- SERUM CA-125 MARKER +VE STATUS

BACKGROUND

- OVARIAN CA IS IMMUNESENSITIVE
- SPECIFIC IMMUNE TX IS POSSIBLE
- DISEASE PROGRESSION CAN BE DELAYED OR STOPPED
- SERUM CA-125 ESTIMATION IS DIAGNOSTIC/PROGNOSTIC

OBJECTIVE

- SERUM CA-125 TEST INDICATES RELAPSE
- CAN BE UTILIZED FOR ESTIMATING EARLY RELAPSE IN TREATED PATIENTS OF FOLLOW-UP
- GENERATING SPECIFIC IMMUNOLOGY MAY PREVENT DISEASE PROGRESSION

OBJECTIVE

- DENDRITIC CELL (DC) – HALLMARK OF IMMUNOLOGY
- MATURE DC – TRANSFORMS 3000-5000 NAÏVE T CELLS INTO COMMITTED T LYMPHOCYTES PER HOUR
- IT HAS POTENTIAL TO GENERATE TRILLIONS OF T CELLS IN ITS LIFE SPAN
- 1MILLION DC IN EARLY STAGE DISEASE IS STANDARDIZED FOR DC THERAPY

METHODS

- PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMC) ARE TRANSFORMED INTO DENDRITIC CELLS OF OUR CHOICE
- TSA/TAA EXPOSURE TRANFORMS imDC TO mDC USED FOR THERAPEUTIC PURPOSE

ADVANTAGE

- PROTOCOL WAS ALREADY IN USE IN ADVANCED STAGE PATIENTS OF VARIOUS CANCERS INCLUDING OVARIAN CA IN OUR CENTER
- TAA/TSA BASED ON OVARIAN CANCER LYSATE (ICTova8 ANTIGEN) HAS BEEN STANDARDIZED

METHODS

- STUDY PLANNED FOR TREATED PATIENTS HAVING EARLY RELAPSE
- CA-125 SERVED AS IMPORTANT MARKER FOR EARLY RELAPSE
- PATIENTS WERE ENROLLED ONLY IF THEY FULFILLED INCLUSION AND EXCLUSION CRITERIA

METHODS- INCLUSION CRITERIA

- RENAL FUNCTION TESTS (WNL)
- LIVER FUNCTION TESTS (WNL)
- PERFORMANCE STATUS ECOG 0-1
- NORMAL THYROID FUNCTION
- NORMAL IMMUNE STATUS
- HIV, HBV, HCV SERO-VE
- FREE FROM RADIATION/CHEMO LAST 1 MONTH

EXCLUSION CRITERIA

- RADIOLOGICAL EVIDENT DISEASE
- MALIGNANT ASCITES
- ACTIVE TUBERCULOSIS
- HEPATOMEGALY
- SPLENOMEGALY
- COLITIS/AUTOIMMUNE DISEASE

END-POINT OF STUDY

- TIME TO RECURRENCE
- OVERALL SURVIVAL INTERVAL
- DISEASE FREE SURVIVAL INTERVAL

WORK-UP

- INFORMED CONSENT
- ULTRASOUND EXAM OF WHOLE ABDOMEN
- CECT, PET-CT (NOT NECESSARY)
- HEMATOLOGY (TLC >7500)
- IF TLC IS LOW S/C G-CSF IS GIVEN 24HRS PRIOR TO BLOOD COLLECTION

METHODS

- PERIPHERAL BLOOD (25-30mL) COLLECTED FROM PATIENT
- HEPARINIZED SYRINGE
- MIXED 1:1 IN CELLNUTE (TRANSPORT) MEDIUM
- SENT TO LAB WITHIN 16 HOURS
- BUFFY COAT SEPERATED AND RUN OVER SURFACE TREATED PLATES

METHODS (Contd.)

- PLATES INCUBATED FOR 2 HRS
- GENTLY WASHED TO REMOVE NON-ADHERENT CELLS
- ADHERENT CELLS CULTURED
- COMPLETE RPMI-1640/GM-CSF/IL-4
- ON 6^{TH} DAY EXPOSED TO ICTova8 ANTIGEN

METHODS (Contd.)

- AFTER 2 DAYS OF EXPOSURE
- CELLS ARE HARVESTED ALONG WITH MEDIUM
- CONFIRMED MATURE DC BY CD 83/86
- VIABLE TEST BY TRYPAN BLUE EXCLUSION CRITERIA (70-80%)
- MYCOPLASMA CONTAMINATION– ELISA
- AEROBIC/ANAEROBIC CULTURE (QUANTIFICATION TEST) – 6 HRS BROTH TEST

METHODS

- MATURE DENDRITIC CELLS ALONG WITH CONDITIONED MEDIUM INFUSED UNDER ONDANSETRONE COVER
- CONTENTS MIXED IN 100 mL OF DNS AND GIVEN I/V IN 15 MINUTES
- REQUIRES NO ADMISSION
- DOMICILIARY TREATMENT PERMISSIBLE AFTER I SUPERVISED DOSE
- SECOND PBMC COLLECTED AFTER 3 WEEKS OF FIRST DOSE
- DOSING EVERY MONTH - SIX MONTHS
- DOSING 6 WK INTERVAL THERE AFTER

ADVERSE EFFECTS

- MOST COMMON A/E ARE (<50%)
- FEVER (<100.4 F) WITHIN ½-2 HRS
- LETHARGY FOR 2-3 DAYS
- BODY ACHE FOR 1-2 DAYS

ADVERSE EFFECTS

- UNCOMMON A/E (<10%)
- FEVER (>/=100.4F) WITH CHILLS & RIGORS
- NAUSEA/VOMITING
- DECREASED APPETITE
- DIARRHOEA
- URTICARIA
- IMMUNE HEMOLYTIC ANEMIA
- COLITIS

ADVERSE EFFECTS

NO PATIENT SHOWED GRADE III/IVA/E INCLUDING

- BRONCHOSPASM
- AUTOIMMUNE ORGAN FAILURE
- HYPOTENSION
- ALLERGY RELATED EDEMA/ANGIOEDEMA
- STEROIDS/ADMISSION
- ANAPHYLAXIS

ADVERSE EFFECTS

- CTCAE GRADES (NCI GUIDELINES)
  - NO A/E (50%)
  - A/E GRADE I (48%)
  - A/E GRADE II (2%)
  - A/E GRADE III (NIL)
  - A/E GRADE IV/V(NIL)

RESULTS

- 26 PATIENTS WERE ENROLLED INTO STUDY BETWEEN 1ST JAN TILL 30TH MARCH 2006
- 20 PATIENTS ARE FREE FROM PROGRESSION – IN MARCH 2008
- 6 PATIENTS – PARTIAL RESPONSE
- 3 PATIENTS LEFT AFTER I YR
- REJOINED AFTER 6 MONTHS

ANALYSIS

- 20 PATIENTS HAVE STABLE CA-125 LEVELS
- RADIOLOGICALLY FREE FROM DISEASE
- PERFORMANCE STATUS REMAINED ECOG 0-1
- TREATMENT IS CONTINUING

ANALYSIS OF 3 PATIENTS WHO LEFT TREATMENT

- 3 PATIENTS LEFT TREATMENT AFTER 1 YEAR OF DCT
- AFTER 4 M - MEDIAN RISE IN CA 125 REACHED TO 800U
- RECEIVED 2-3 CYCLES OF CHEMOTHERAPY
- RETURNED TO RECEIVE DCT AND CONTINUING TREATMENT

ANALYSIS OF PARTIAL RESPONDERS

- 6 PATIENTS SHOWED PARTIAL RESPONSE
- CA-125 LEVEL KEPT INCREASING AND OPTED FOR CHEMOTHERAPY AFTER 3 MONTHS OF DCT
- RECEIVED 6 DOSES OF CHEMOTHERAPY
- NOT DEVELOPED RADIOLOGICAL DISEASE

CONCLUSION

- DC THERAPY – SAFE
- HIGHLY EFFECTIVE IN PREVENTING RELAPSE IN OVARIAN CANCERS ASSOCIATED WITH CA-125 MARKER POSITIVITY
- PROLONGS DISEASE FREE SURVIVAL
- IMPROVES OVERALL SURVIVAL
- MAINTAINS QUALITY OF LIFE

CONCLUSION (MERITS)

- GOOD COMPLIANCE
- PATIENTS NEVER REFUSED TREATMENT
- REPRODUCIBLE PROTOCOL
- STANDARDIZED PROTOCOL
- PATIENTS NEED NOT TRAVEL TO LAB
- NO IMMEDIATE OR LATE A/E

CONCLUSION

- DENDRITIC CELL THERAPY IS USEFUL IN LOW DISEASE THRESHOLD
- REQUIRES PHASE III MULTICENTRIC AND RANDOMIZED TRIALS TO BE ADOPTED INTERNATIONALLY
- BEST UTILIZED IN CONJUNCTION WITH STANDARD THERAPY

THANK YOU

OUR GRATITUDE TO

AMIM CANCER TRUST

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