

RADIOTHERAPY IN ACUTE LEUKEMIAS



RADIATION THERAPY IN ALL

- PROPHYLACTIC CRANIAL IRRADIATION
- THERAPEUTIC CRANIAL IRRADIATION
- THERAPEUTIC CRANIAL AND NEURAXIS RADIATION
- TESTICULAR IRRADIATION
- MEDIASTINAL IRRADIATION
- TOTAL BODY IRRADIATION – BMT CONDITIONING



COMBINED MODALITY WHY ?

- CSF FORMATION IN BRAIN VENTRICLES BY CHOROID PLEXUS-IVF-CEREBRAL AQUEDUCT TO 4TH VENTRICLE COMMUNICATES WITH SUB ARACHNOID SPACE-CSF RESORPTION BY ARACHNOID VILLI IN THE DURAL SINUSES.
- IT THERAPY THEROTICALLY UNDERTREATS THE VENTRICULAR SPACES AND CEREBRAL AND CEREBELLAR SULCI AND GROSS DISEASE EXTENDING TO BRAIN SUBSTANCE
- CRANIAL RT WITH IT,LATER COVER THE SPINAL SUBARACHNOID SPACE
- REDUCTION OF THE SPINE DOSE THAN BRAIN DURING CSI FOR MENINGEAL LEUKEMIA

NEJM 1975



DEFINITION OF RISK GROUPS

ALL BFM 95

- **STANDARD RISK (6 CRITERIA)**
- PREDNISONE GOOD RESPONSE (BLASTS <1000 /MICROLIT OF PERIPHERAL BLOOD ON DAY 8) AFTER A 7 DAY PREDNISONE PREPHASE (PRED-GR)
- WBC <20,000/MICRO LIT AND AGE >1-<6 YEARS
- A COMPLETE REMISSION ON DAY 33 (M1-MARROW)
- NO TRANSLOCATION t(9:22) OR BCR/ABL RECOMBINATION
- NO TRANSLOCATION t(4:11) OR MLL /AF 4 RECOMBINATION
- NO T – IMMUNOLOGY

MEDIUM RISK GROUP (4+1 or more)

- LEUKEMIC CELLS <1000/MICROLIT IN THE PERIPHERAL BLOOD ON DAY 8(PREDNISON-GR)
- COMPLETE REMISSION ON DAY 33(M1-MARROW)
- NO TRANSLOCATION t (9:22) OR BCL/ABL RECOMBINATION
- NO TRANSLOCATION t(4:11) OR MLL/AF 4 RECOMBINATION
- LEUKOCYTES MORE THAN 20,000 /MICROLIT,AGE LESS THAN ONE YEAR OR MORE THAN 6 YEARS



HIGH RISK GROUP(**EVERY CRITERION**)

- MORE THAN 1000/ MICROLIT LEUKEMIC CELLS IN PERIPHERAL BLOOD ON DAY 8 (PRED=PR)
- NO COMPLETE REMISSION ON DAY 33
- TRANSLOCATION t(9:22) OR BCR/ABL RECOMBINATION
- TRANSLOCATION t(4:11) OR MLL/AF4 RECOMBINATION



DEFINITION OF CNS STATUS

- **CNS STATUS 1(NEGATIVE):**
-
- NO CLINICAL EVIDENCE OF A CNS DISEASE
- NO IMAGING-CT/MRI -EVIDENCE OF CNS LESION
-
- NORMAL FUNDOSCOPIC FINDING
-
- BLAST FREE CSF



DEFINITION OF CNS STATUS

- **CNS STATUS 2 (NEGATIVE):**
- BLASTS UNAMBIGUOUSLY IDENTIFIED, RBC:WBC <100:1 ON CYTOSPIN PREPARATION OF CSF WITH A CELL COUNT OF <5/MICROLIT- NON TRAUMATIC UN CONTAMINATED CSF
- BLASTS IDENTIFIED, RBC:WBC >100:1 ON CYTOSPIN PREPARATION OF CSF- TRAUMATIC BLOOD CONTAMINATED CSF
- TRAUMATIC LP (BLOOD CONTAMINATED CSF)

ALL IC BFM 2002



DEFINITION OF CNS STATUS

- **CNS STATUS 3(POSITIVE)**
- A MASS LESION IN THE BRAIN AND OR MENINGES ON CT/MRI
- CRANIAL NERVE PALSY UNRELATED TO OTHER ORIGIN EVEN IF THE CSF IS BLAST FREE OR NO CIRCUMSCRIBED SPACE OCCUPYING LESION ON MRI/CTSCAN
- PURE RETINAL INVOLVEMENT WITH BLAST FREE CSF AND NO MASS ON CT/MRI
- NON TRAUMATIC LP WITH A CSF CELL COUNT OF >5/MICROLIT

ALL IC BFM 2002



CRANIAL PROPHYLAXIS - ALL

- **ALL-BFM 83**- 12 GY OF PREVENTIVE CRT WAS AS EFFECTIVE AS 18 GY OF HIGH- SRG
- **ALL-BFM 90**- REDUCTON OF LONG TERM MORBIDITY IN PRED-GR PATIENTS BY LIMITING RADIATION DOSE -12 GY TO MR-ALL AND HR
- **ALL -86 TO 90**-IN CRITICAL GROUPS INCIDENCE OF CNS RELAPSE WAS LESS THAN 5 %.ESPECIALLY WITH HD-MTX AND MTX -IT INCIDENCE WAS LESS THAN 3 %
- **ALL-BFM-90**-12 GY INSTEAD OF 18 GY PROVIDED EQUALLY EFFICIENT CNS PROPHYLAXIS IN HIGH RISK GROUPS HAD PGR
- **AMERICAN STUDIES** –MR PATIENTS WITH T-ALL HAD HIGHER INCIDENCE OF SYSTEMIC AND CNS RELAPSE IN NON IRRADIATED PATIENTS

ALL-BFM 95



CRANIAL PROPHYLAXIS

- CHILDREN AND ADOLESCENTS (<18YRS) WITH **MEDIUM RISK GROUP WITH T-ALL AND ALL HIGH RISK GROUP PATIENTS**
- NO RT FOR STANDARD RISK AND MEDIUM RISK PATIENTS (EXCEPT T -ALL)
- DOSAGE :AGE- LESS THAN ONE YEAR-NO RT
AGE- ONE YEAR OR MORE -**12GY**



CRANIAL PROPHYLAXIS - ST JUDES CH

- With effective risk-adjusted chemotherapy, prophylactic cranial irradiation can be safely omitted from the treatment of childhood ALL
- Risk factors for CNS relapse included the genetic abnormality $t(1;19)$ (*TCF3-PBX1*), any CNS involvement at diagnosis, and T-cell immunophenotype

NEJM 2009



CRANIAL PROPHYLAXIS-ADULTS

- Central Nervous System Recurrence Rate in Adult Acute Lymphoblastic Leukemia- Cancer May 15, 2010

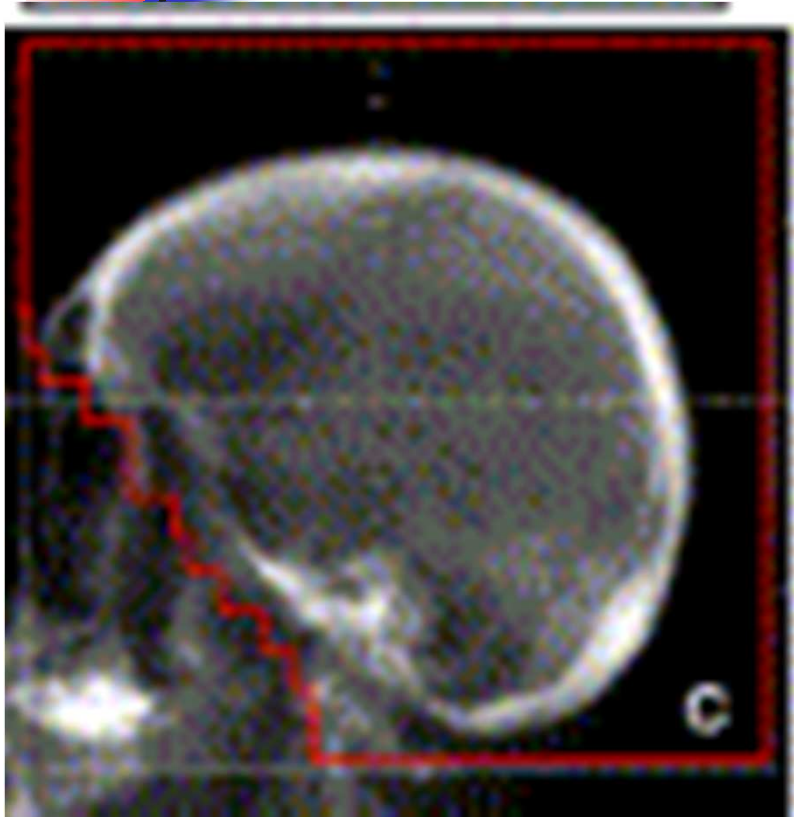
PROTOCOL	CNS RELAPSE	PROPHYLAXIS
HYPERCVAD	4%	NO RT
BFM	1%	18GY
AUG BFM	1%	18GY
CALGB	11%	24GY



CRANIAL IRRADIATION

- **DOSAGE**
- CHILDREN LESS THAN ONE YEAR- NO IRRADIATION
- ONE TO TWO YEARS -12 GY
- MORE THAN 2 YEARS-18 GY
- ADULTS 24-30Gy

Cranial Irradiation Technique



- **High voltage conditions with Co -60 or LA**
- **Photon energies of 6MV or less**
- **Photon energies more than 6 MV should not be used so that the build up region at initial depth is superficial to the meninges.**
- **Daily set up-mask technique**
- **Irradiation volume-**
 - **Whole neurocranium with both upper vertebra (c2),**
 - **Retrobulbar tissue and**
 - **Complete cranial base with its middle cranial groove.**



CRANIAL IRRADIATION TECHNIQUE

- EVERY FIELD SHOULD BE TREATED IN EVERY SESSIONS
- DAILY SINGLE DOSE IS 1.5 GY .THIS IS ADMINISTERED IN 5 SESSIONS PER WEEK UNTIL THE TOTAL DOSE HAS BEEN APPLIED
- ANGULATION OF THE BEAM (3-5 DEG POSTERIOR), HALF BEAM- TO AVOID OPHTHALMOLOGICAL COMPLICATIONS



NEURAXIS IRRADIATION

- INDICATIONS-OVERT CNS LEUKEMIA IN ADULTS UNSUITABLE FOR CHEMOTHERAPY, ISOLATED CNS RELAPSE.
- DOSAGE- TO THE CRANIUM -24 TO 30 GY. TO THE SPINE-15 TO 18GY. 1.5 TO 1.8 GY /FRACTION.



CRANIOSPINAL RADIATION

- SURVIVAL OUTCOME FOLLOWING ISOLATED CENTRAL NERVOUS SYSTEM RELAPSE TREATED WITH ADDITIONAL CHEMOTHERAPY AND CRANIO SPINAL IRRADIATION IN CHILDHOOD ACUTE LYMPHOBLASTIC LEUKEMIA-**IJRBP 1995**
- Low-Dose, Monthly Craniospinal Irradiation for Central Nervous System Relapse of Pre B-Cell Acute Lymphoblastic Leukemia in Children: The University of Pennsylvania Experience-**IJRBP2004**



CRANIOSPINAL RADIATION

- The Role of Craniospinal Irradiation in Adults with a Central Nervous System Recurrence of Leukemia-
***Cancer* 2004;100:2176–80.**

NERURAXIS IRRADIATION



- FIELDS-LATERAL PARALLEL OPPOSED CRANIAL FIELDS,POSTERO-ANTERIOR SPINAL FIELDS
- COUCH AND GANTRY ROTATION-TO MATCH THE FIELDS
- MAXIMUM BEAM ENERGY 6 MV



TESTICULAR INVOLVEMENT

- **INITIAL TESTICULAR INVOLVEMENT**-RECENT OCCURRENCE OF A PAINLESS SWELLING OF THE TESTES WITHOUT SIGNS OF INFECTION, THEN A SONOGRAPHICAL EXAMINATION OF BOTH TESTES IS NECESSARY AND A BIOPSY IS NOT NECESSARY.
- **IF UNCERTAINTY EXISTS**- ILLNESS INVOLVING INFECTION OR VASCULAR CHANGES OF THE TESTIS SHOULD BE RULED OUT AND A TESTIS BIOPSY SHOULD BE PERFORMED.



TESTICULAR INVOLVEMENT

- **MANAGEMENT**-IN THE CASE OF TESTICULAR INVOLVEMENT NO UNILATERAL OR BILATERAL ORCHIDECTOMY IS PLANNED.
- IF THE TESTICLE SIZE NORMALIZES COMPLETELY AFTER THE PROTOCOL AT THE LATEST ACCORDING TO TACTILE AND SONOGRAPHIC FINDINGS THERE IS NO EXTRA TESTICULAR IRRADIATION.
- IF AFTER THE PROTOCOL A DOUBTFUL CLINICAL FINDINGS REMAINS, BIOPSY IS REQUIRED AND IN CASE OF INVOLVEMENT LOCAL IRRADIATION MUST BE APPLIED.



TESTICULAR IRRADIATION

- UNILATERAL IRRADIATION OR ORCHIDECTOMY AS LOCAL MANAGEMENT WAS FELT TO BE ASSOCIATED WITH A SIGNIFICANT RISK OF CONTRALATERAL DISEASE JUSTIFYING TREATMENT DIRECTED AT BOTH TESTIS FOR LEUKEMIA MANAGEMENT.
- 24 TO 30 GY OVER 2 TO 3 WKS(200CGY-300CGY/#) (ALL BFM 95)
- 18 GY IN 10 FRACTIONS OVER TWO WEEKS –(ALL IC 2002)



TESTICULAR IRRADIATION

- Overt testicular disease at diagnosis of childhood acute lymphoblastic leukemia: lack of therapeutic role of local irradiation - *Leukemia* (2005) 19, 1399–1403
- The predictive strength of overt testicular disease in childhood ALL has diminished in recent years because of the use of contemporary risk-stratified and intensified systemic chemotherapy that has included high-dose methotrexate.
- Local irradiation of the testes in patients with overt testicular disease at diagnosis appears to be unnecessary for achievement of survival rates comparable to those of patients without testicular disease



TESTICULAR RELAPSE

- TESTICULAR RELAPSE-UNILATERAL OR BILATERAL PAINLESS BUT HARD SWELLING OF THE TESTIS (VOLUME >2) AND A BIOPSY SHOULD BE DONE.
- COMMON WITH T CELL ALL
- USUALLY FOLLOWS SYSTEMIC AND CNS RELAPSE
- POOR PROGNOSTIC FACTOR
- 1970-5%-15%
- WITH HD MTX-<2%
- **MANAGEMENT**:BOTH INTENSIVE SYSTEMIC THERAPY AND LOCAL RADIOTHERAPY(18Gy in 9#)UKALL R3

TESTICULAR IRRADIATION



- TESTICULAR IRRADIATION IS ADMINISTERED VIA A SINGLE ANTERIOR PORTAL WITH THE USE OF ELECTRON BEAM OF APPROPRIATE ENERGY OR LOW ENERGY PHOTONS
- PATIENT IN A SUPINE POSITION AND THE PENILE SHAFT TAPPED UP AND OVER THE SYMPHYSIS PUBIS
- RECTANGULAR FIELD WITH MINIMUM OF 5 MM MARGIN TO THE SCORUM (INCLUDES BOTH TESTIS AND EPIDIDYMIS)



TESTICULAR IRRADIATION

- 10X10 CMS CONE PROVIDES ADEQUATE COVERAGE
- MOST APPROPRIATE ELECTRON ENERGY -9 TO 12 MEV
- A POLYSTYRENE /LEAD BLOCK IS USED TO SUPPORT TESTIS AND SHIELD THE PERINEUM
- SKIN APPOSITION OF THE BEAM CAN BE ACHIEVED BY ANGLING THE GANTRY



TESTICULAR IRRADIATION

- IN THE ABSENCE OF ELECTRON BEAMS LOW ENERGY PHOTONS CAN BE USED(4 TO 6 MV).
- TO ACHIEVE DOSE HOMOGENICITY .5 TO 1 CMS OF BOLUS OVER THE ENTIRE SCROTAL AREA MAY BE NECESSARY.
- SHIELDING OF THE UNDER LYING PERINEAL TISSUE IS PROBLAMATIC
- THE EXIT DOSE WILL BE HIGH.



MEDIASTINAL IRRADIATION

- IF A MEDIASTINAL TUMOR RECEDES <30% OF ITS ORIGINAL SIZE BY DAY 33 (MEASUREMENT CRITERIA –MAXIMAL DIAMETER TAKEN AT D5), THEN PHASE II OF THE SAME PROTOCOL IS TO BE CONTINUED.
- IF THE MEDIASTINAL TUMOR HAS NOT COMPLETELY RECEDED BY DAY 33 (REMAINING TUMOR >30% OF ORIGINAL SIZE), THEN THE PATIENT IS PLACED IN THE HR BRANCH.
- IF ANY RESIDUAL TUMOR REMAINS IN THE CT /MRI AFTER A WEEK OF PROTOCOL THAT CAN BE RESECTED FOR HPE AND MOLECULAR GENETICS

ALL BFM 95



MEDIASTINAL IRRADIATION

- IF NO VITAL INFILTRATES ARE FOUND CONTINUE IN THE SAME BRANCH. IF VITAL INFILTRATES ARE FOUND CONSIDER MEDIASTINAL IRRADIATION.
- DOSE-30-40 GY
- ALL T CELL PHENOTYPE WILL RECEIVE CONSOLIDATION RT.

ALL BFM 95



TOTAL BODY IRRADIATION- BMT CONDITIONING

- TBI-CYTOTOXIC AND IMMUNOSUPPRESSIVE AGENT.
- ELIMINATE RESIDUAL LEUKEMIA AND EQUALLY EFFECTIVE IN MEDULLARY AND EXTRAMEDULLARY REGION.
- IT PERMITS ENGRAFTMENT OF DONOR IMMUNE AND HAEMATOPOIETIC CELLS.THE DONOR IMMUNE CELLS GENERATE THE GRAFT VERSUS LEUKEMIA EFFECT, AN IMPORTANT COMPONENT IN THE ERADICATION OF HOST LEUKEMIA.



TOTAL BODY IRRADIATION

- ALLOGENIC TRANSPLANT-ALL IN SECOND REMISSION AFTER AN EARLY RELAPSE,HIGH RISK ALL (PH +) AFTER FIRST REMISSION
- DOSE-200 CGY GIVEN IN BID WITH 6 HOUR INTER FRACTION INTERVEL 3 DAYS TO THE TOTAL DOSE OF 12 GY .DOSE RATE AVERAGE 8 TO10 CGY PER MINUTE(MAXIMUM UP TO 15 CGY).
- IN HR PATIENTS CNS POSITIVE DISEASE CRANIAL BOOST- 12 GY,TESTICULAR BOOST IN CASE OF INVOLVEMENT 18GY A WEEK PRECEDING THE TBI-ALL BFM 2002



SEQUAE OF TREATMENT

- CNS IRRADIATION:(24 GY vs18 GY VS MTX) SOMLONENCE SYNDROME,PITUITARY DYSFUNCTION,COGNTIVE FUNCTION DEFECTS,LEUKOENCHEPHALOPATHY,SECONDARY MALIGNANCIES
- TESTICULAR IRRADIATION:STERILITY,LEYDIG CELL DYSFUCTION (RARE).



SUMMARY

- **ROLE OF RT IN ALL:**
 - CRANIAL PROPHYLAXIS(MRG-T CELL ALL,HRG)
 - CRANIAL TREATMENT (ALL CNS INVOLVEMENT)
 - CRANIOSPINAL IRRADIATION (OVERT CNS INVOLVEMENT IN ADULT ALL,ISOLATED CNS RELAPSE)



SUMMARY

- TESTICULAR IRRADIATION (RESIDUAL,RELAPSE)
- MEDIASTINAL IRRADIATION (RESIDUAL,T CELL ALL,RELAPSE)
- TOTAL BODY IRRADIATION (SECOND REMISSION AFTER EARLY RELAPSE,HIGH RISK WITH FIRST REMISSION)



ROLE OF RT IN AML



HYPERLEUCOCYTOSIS -HISTORICAL

- Role of cranial radiotherapy 250cGy in 2 fraction-
Blood Vol No:2 1982
- CRT doesn't impact survival -AJH 2007
- No role of RT –Cancer 2008



GRANULOCYTIC SARCOMA

- Isolated extramedullary form of AML
- Common with M4,M5
- Symptomatic areas-Orbit, spinal cord
- Dose 4 GY to 30Gy in 2 to 15 fractions with 2-3 cm margins depends upon the size of the tumor

Cancer 1981



CRANIAL PROPHYLAXIS

- Not well defined for AML
- CNS relapse rates infrequent <5%
- High WBC at diagnosis ,monocytic variant – common causes for CNS relapse



CRANIAL RADIATION

- MRC AML trials 8 TO 12 from 1978 to 2002
- MRC AML trials have never employed cranial irradiation, but delivered intrathecal chemotherapy alone and the low incidence of isolated and combined CNS relapses challenges the use of cranial irradiation with its long-term sequelae.

Leukemia (2005) 19, 2130–2138



CRANIAL RADIATION

- A specific characteristic of the BFM trials is the general use of prophylactic CNS irradiation.
- Only AML-BFM 87 compared patients with and without CNS irradiation. Results indicated that CNS irradiation is an essential therapy element of the BFM protocols. Outcome was inferior in the no irradiated groups, especially due to bone marrow recurrences, but also due to higher incidence of isolated or combined CNS relapses.



CRANIAL RADIATION

Results suggested that chemotherapy alone could destroy leukaemic blasts in the bone marrow, but with less success in the CNS. Residual blasts from the CNS may reseed the bone marrow and lead to bone marrow relapses. Therefore, CNS irradiation has remained a therapy element in the AML-BFM studies.



CRANIAL RADIATION

- Dose > 3Years 18Gy
1-3 Years 15 Gy
Less than 1 year No radiation
- With or without CNS involvement after complete remission
- Mandatory for all with high counts 70,000/microL with or with out initial CNS involvement



TOTAL BODY IRRADIATION-HIGH DOSE

- Allogeneic Stem Cell Transplantation for Acute Myeloid Leukemia in First Complete Remission: Systematic Review and Meta-analysis of Prospective Clinical Trials
- Ablative conditioning regimen 10-14 Gy of TBI

JAMA. 2009;301(22):2349-2361

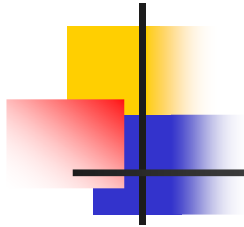


TOTAL BODY IRRADIATION-LOW DOSE

- Nonmyeloablative Allogeneic Hematopoietic Cell Transplantation in Patients With Acute Myeloid Leukemia –Low dose **2 Gy TBI** with Fludarabine for old and infirm patients with AML –**JCO May 2010**
- Treatment for Acute Myelogenous Leukemia by Low-Dose, Total-Body, Irradiation-Based Conditioning and Hematopoietic Cell transplantation From Related and Unrelated Donors- Low dose **2 Gy TBI** with Fludarabine for older patients with **AML-JCO MAY 2006**



THANK YOU



- **Table 1. Cumulative risk of isolated central nervous system (CNS) relapse according to CNS1 or 2 status in selected clinical trials.**
- **Study Patient % Cumulative Risk**
- **Study (Reference) Period Group CNS1 CNS2 P value**
- SJCRH XI 8 1984-1988 All 4.0 13.0 < 0.001
- POG 8602 9 1986-1990 B-lineage 5.3 11.6 0.002
- BFM 95 10 1995-1999 All 3.5 10 < 0.05
- CCG 1800/1900 11 1988-1993 All 3.9 7.7 0.0018
- EORTC 58881 12 1989-1998 All 8.1 15.7 —
- CCG 105 13 1983-1989 Non-irradiated 6.5 11.8 0.15
- CCG 105 13 1983-1989 Irradiated 6.4 2.3 0.32
- DCLSG ALL-7 & 8 14 1988-1997 All 3.6 5.4 NS
- SJCRH XIIIB 15 1994-1998 All 0.7 3.9 0.09