TOTAL MARROW IRRADIATION

Renzo Corvò
National Cancer Research Institute
and University of Genoa
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1907</td>
<td>X Ray Bath</td>
<td></td>
</tr>
<tr>
<td>1940-1950</td>
<td>Lymphoma/solid tumors with disseminated disease</td>
<td></td>
</tr>
<tr>
<td>1960</td>
<td>First exploration for bone marrow transplantation</td>
<td></td>
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<tr>
<td>1970-1980</td>
<td>TBI with low-dose</td>
<td></td>
</tr>
<tr>
<td>1977</td>
<td>TBI myeloablative</td>
<td>TBI sub-myeloablative</td>
</tr>
<tr>
<td>2005</td>
<td>NEW!</td>
<td>Total Marrow Irradiation (conformal TBI)</td>
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</tbody>
</table>
BLOOD STEM CELL TRANSPLANT

Cyclophosphamide plus
Total Body Irradiation - TBI
↓
“leukemic cell killing”
“immunosuppressive role”
“making space in bone cavities”
↓

ALLOGENEIC TRANSPLANT

from
matched siblings
unmatched siblings
matched unrelated donors (MUD)
1977: first TBI in Genoa

more than 2600 patients submitted to TBI in Genoa
TBI schedules in Genoa

**TBI myeloablative**

→ 990 cGy / 3 fractions / 3 days

→ 1200 cGy / 6 fractions / 3 days (with 6 hour inter-fraction interval)

Corvò R et al, Bone Marrow Transplant, 2002
MORE RADIATION DOSE
= 
MORE LEUKEMIC CELL KILLING
= 
MORE RADIATION INDUCED EFFECTS
→
NO IMPROVEMENT IN SURVIVAL
ORGANS at RISK

Parotid
Kidney
Liver
Heart
Eyes

OARs

RISK FOR TOXICITIES
### ACUTE AND LATE TBI-INDUCED TOXICITIES

<table>
<thead>
<tr>
<th>Biological Effects</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>kidney failure</td>
<td>5-15%</td>
</tr>
<tr>
<td>intestinal pneumonitis</td>
<td>5-15%</td>
</tr>
<tr>
<td>cataract</td>
<td>4-22%</td>
</tr>
<tr>
<td>growth delay</td>
<td>40-90%</td>
</tr>
<tr>
<td>amenorrhea</td>
<td>90%</td>
</tr>
<tr>
<td>azoospermia</td>
<td>95%</td>
</tr>
<tr>
<td>veno-occlusive disease</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>cognitive deficits</td>
<td>&lt;20%</td>
</tr>
<tr>
<td>neurological complications</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>hypothyroidism</td>
<td></td>
</tr>
<tr>
<td>subclinical</td>
<td>25-43%</td>
</tr>
<tr>
<td>clinical evident</td>
<td>3-13%</td>
</tr>
</tbody>
</table>
Second Critical Issue!

No dose distribution in 2010!
Total Marrow Irradiation
Contouring

- **Target**
  - bone marrow sites:
    - head (cranium, mandible)
    - upper limb girdle
    - sternum
    - ribs
    - vertebrae
    - pelvis ox
    - lower limb girdle
    - spleen
    - (leukemic bulk)

- **OARs**
  - lungs
  - spine
  - eyes, larynx, oral mucosa
  - heart, breasts, esophagus
  - liver
  - kidneys
  - brain
  - testes
  - thyroid
  - parotids
  - bowel / bladder / rectum
Preliminary clinical experience
@ IST Genoa

TOTAL MARROW IRRADIATION - TMI
with Helical Tomotherapy
Radiation Dose Scheduling

Day 1
- TBI 200 cGy (x2)

Day 2
- TBI 200 cGy (x2)

Day 3
- TBI 200 cGy (x2)

Day 4
- TMI 200 cGy (x1)

TBI + TMI = 1400 cGy

time

coronal view

TMI - coronal view

sagittal view

TMI - sagittal view
Sequence TBI $\rightarrow$ TMI

- **TBI for allograft**: excellent results in acute leukemia in early stage of disease with low toxicity

- **TMI**: in advanced leukemia may be the best way to increase the TBI dose without increasing radiation-induced toxicity
Steps for TMI delivery

- **Patient set-up** (immobilization systems, field junction between upper TMI and lower TMI)
- CT scan from vertex to feet
- **Contouring** CTVs, OARs and VOIs
- **Dosimetric Planning** (CTV → PTV = 5 mm)
- Physical dose verify
- **Patient set-up verify with IGRT-MV**
- **TMI delivery** (upper and lower) con IMRT
Treatment technique

- **Upper body TMI (UTMI)** = from vertex to knees
- **Lower body TMI (LTMI)** = from knees to tip of the feet
- **UTMI and LTMI plans** are properly matched in terms of dose uniformity

Full Helical TMI Dose

UTMI and tLTMI plans can be summed on the same CT data set

Zeverino et al. EMEA 2010 Malaga
TMI-DVH - dose 200 cGy
Dose Volume Histograms – TBI plus TMI

**TBI**

**Entire Target Receives Full Dose**

**Critical Organ Receives Full Dose**

**Lungs**

20% less

**Typical TBI Dose Volume Histogram**

**TMI**

Entire target STILL receives full dose

Critical Organ receives LESS dose

**TMI – H&N**

**TMI – Body**

**DVH Legend**

- Brain
- Bone
- Lungs
- Oral mucosa
- Parotid dx
- Parotid un
- Tongue

**Dose-Volume Histogram - Cumulative Mode Relative**

- Relative Volume (% Normalized)
- Dose (Gy)
Organ sparing and marrow coverage

- Organ sparing is achievable in terms of **median dose reduction** (i.e. dose delivered to 50% of organ volume)
- Amount of dose reduction is independent from fractionation
- Small organs are penalized because of technical parameters of treatment
- Optimal PTV coverage and homogeneity

<table>
<thead>
<tr>
<th>Organ</th>
<th>Median Dose reduction</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain</td>
<td>45.5%</td>
<td>4.6%</td>
</tr>
<tr>
<td>Left Parotid</td>
<td>30.3%</td>
<td>11.5%</td>
</tr>
<tr>
<td>Right Parotid</td>
<td>29.6%</td>
<td>10.3%</td>
</tr>
<tr>
<td>Oral Mucosa</td>
<td>35.8%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Larynx</td>
<td>56.4%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Thyroid</td>
<td>43.3%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Left Lung</td>
<td>44.3%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Right Lung</td>
<td>47.5%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Heart</td>
<td>45.1%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Liver</td>
<td>47.0%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Left Kidney</td>
<td>56.8%</td>
<td>5.2%</td>
</tr>
<tr>
<td>Right Kidney</td>
<td>60.5%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Bowel</td>
<td>52.7%</td>
<td>3.4%</td>
</tr>
<tr>
<td>Male Gonads</td>
<td>80.7%</td>
<td>12.3%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bone Marrow -PTV</th>
<th>Value</th>
<th>Mean (%)</th>
<th>Range (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D95</td>
<td>93.3</td>
<td>91.9 - 94.2</td>
<td></td>
</tr>
<tr>
<td>D90</td>
<td>95.7</td>
<td>94.1 - 96.7</td>
<td></td>
</tr>
<tr>
<td>D5</td>
<td>102.9</td>
<td>101.7 - 103.8</td>
<td></td>
</tr>
</tbody>
</table>

Legenda:
- D95 = dose received by 95 % of Planned Target Volume (PTV)
- D90 = dose received by 90 % of PTV volume
- D5 = dose received by 5 % of PTV volume
**TMI- DVH OARs – dose 200 cGy**

- **Median doses to OARs:**

  - **lungs**: 100 cGy (50%)
  - **liver**: 110 cGy (45%)
  - **kidneys**: 81 cGy (60%)
  - **brain**: 117 cGy (42%)
  - **parotids**: 165 cGy (18%)
TMI-DVH OARs – dose 200 cGy

- Median doses to OARs:
  - heart 111 cGy (- 45%)
  - thyroid 144 cGy (- 28%)
  - bowel 96 cGy (- 52%)
  - larynx 85 cGy (- 57.5%)
  - testes 40 cGy (- 80%)

  Dose to Body (by excluding OARs):
  - 157 cGy (- 22%)

Delivery Time for upper TMI

According to parameters optimization (Field Width, Pitch e Modulation Factor):

→

we can obtain an overall treatment time of 19.5 min for delivery 200 cGy.
Total body irradiation (TBI) and total marrow irradiation (TMI) for patients with advanced hematologic malignancies undergoing an allogeneic stem cell transplant (HSCT) : a pilot study

R Corvo’, S.Agostinelli, M.Zeverino, S.Barra ,MT Van Lint, F Frassoni, T Lamparelli, G. Taccini, A. Bacigalupo

Divisione Ematologia e Trapianto di Midollo Osseo, Ospedale San Martino ;Istituto Nazionale per la Ricerca sul Cancro- Genova

Presented at EBMT Group – Vienna- 2010
Presented at ESTRO – Barcellona- 2010
Presented at ASTRO – San Diego - 2010
Submitted to Radiotherapy & Oncology- 2010
Submitted to Int J Radiat Oncol Biol - 2010
The Genoa experience
in allogeneic stem cell transplantation

- From June 2009 to August 2010
- 15 patients with relapsed acute leukemia
- TBI 12 Gy/ 6 fx → TMI 2 Gy/ 1 fx: 14 Gy/7 fx
- Median follow-up: 210 days (80-385 days)
- All patients reached Complete Remission
- 3 (20%) deaths for GvHD (2) and infection (1)
- 2 (15%) relapses (in 2 previous autografted pts)
- 10 (67%) alive in remission
CONCLUSIONS

Early encouraging outcomes also in patients with very advanced disease, having failed a first allogeneic or autologous transplant.

- Early tolerance is excellent with TBI/TMI 14 Gy
- Allogeneic Transplant:
- dose finding study?
- Autologous Transplant:
- new trial design
TMI: potentials

- TMI as upfront (hard task!)
- TMI *boost* for escalating-dose after TBI in patients with advanced leukemia:

**TBI 2 Gy/ 6 fr/ 3 days + TMI with dose escalation:**

- **1° step** → **16 Gy/ 8 fr/ 4 days** (6 pts)
- **2° step** → **18 Gy/ 8 fr/ 4 days** (6 pts)
- **3° step** → **20 Gy/ 8 fr/ 4 days** (6 pts)
Ringraziamenti

- Andrea Bacigalupo, Francesco Frassoni (A.O.U. San Martino, Genoa)
- Salvina Barra, Stefano Vagge (IST)
- Personale TSRM (IST)
- S.C. Fisica Medica –IST: S.Agostinelli, M.Zeverino, G.Taccini
MEETING IN GENOA
on TMI in autograft
19 January 2011