Total Body Irradiation (TBI): Past, Present, and Future

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Disclosures

• No conflicts of interest
Overview

• Early use of TBI
• Outcome data for modern TBI vs Chemotherapy only regimens
• TBI Technical factors
  – Fractionation
  – Dose
  – Dose rate
  – Lung blocking
• TBI Technique
• Future directions
Earliest Description of TBI

Fredrich Dessauer, Frankfurt, 1905
A PRELIMINARY REPORT ON CONTINUOUS IRRADIATION OF THE ENTIRE BODY

By ARTHUR C. HEUBLEIN, M.D., Hartford, Connecticut

The purpose of this paper is to present a new method of X-ray therapy consisting of continuous irradiation of the entire body at long distances from the tube. The following considerations have led the writer to the belief that this method may prove valuable in the treatment of certain excites a favorable reaction on the part of the body as a whole. The nature of this reaction is complex and the factors are largely unknown. It is probably of much importance in the cure of malignant tumors by radiation.” He further states, “The immediate improvement in health and

Technique and initial outcome (20 patients)
“Heublein Unit” Memorial Hospital, New York

- Lead-lined room
- Coolidge tube
  185 KV x-rays
- 4 beds
  - 730 & 550 cm
- Canary

Radiology, 18:1051, 1932
“Heublein Unit” Memorial Hospital, New York

- Dose escalated from 40-225 r
- 20 hours per day
- For 190 r:
  - 7.5 or 13.9 days
- Canary
  - Died after 5250 r
  - “marked radiation changes”
TOTAL BODY IRRADIATION
WITH REVIEW OF CASES
By FRED G. MEDINGER, M.D.,* and LLOYD F. CRAVER, M.D.
From the Memorial Hospital
NEW YORK, NEW YORK

FOR many years, the oncologist has sought a method of therapy whereby cancer widely disseminated through the regression of tumor masses in animals by smaller doses of generalized irradiation than was possible by local treatment. Mun-

N=270

Modest palliative effect seen
Maximum Tolerated Dose: 300 r over 10 days
Early Modern Era:

TBI for Lymphocytic Malignancies
## Palliation of Lymphoid Malignancies

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Grade (stage)</th>
<th>% CR</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NCI</strong> Johnson, 1978</td>
<td>TBI 300cGy (10/fx) vs CVP 4-10 cycles</td>
<td>High and Low (III, IV)</td>
<td>83 vs 54 0.01</td>
</tr>
<tr>
<td><strong>British 1981</strong></td>
<td>TBI 150cGy (10/fx) vs CHOP x 6</td>
<td>High (III, IV)</td>
<td>23 vs 39 ns</td>
</tr>
<tr>
<td><strong>U. Cape Town Jacobs, 1987</strong></td>
<td>TBI 150cGy (15/fx) vs Chloramb - Pred</td>
<td>Low (III,IV) + CLL</td>
<td>59 vs 52 ns</td>
</tr>
</tbody>
</table>

TBI with this regimen: myelosuppression but no nausea
Myeloablative TBI for Myeloid Leukemia
• 19 patients Acute Myelogenous Leukemia
• Cytoxan and TBI: 920 cGy single dose “opposing” $^{60}$Co sources.
• Myeloablative treatment
• Donor marrow infusion for “rescue”

Thomas et al NEJM 301:597, 1979
• Only 1 patient relapsed (5%)
• But 5 died of “interstitial pneumonia”
• Important advance in curative therapy of AML

Thomas et al NEJM 301:597, 1979
# TBI-Cytoxan vs Busulfan-Cytoxan Randomized trials

<table>
<thead>
<tr>
<th>Diagnoses</th>
<th>TBI</th>
<th>TBI Dose Rate cGy/min</th>
<th>Lung dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nordic Ringden, 1994</td>
<td>AML/CML</td>
<td>10 Gy in 1 12 Gy in 3-7</td>
<td>4 4-13</td>
</tr>
<tr>
<td>French Blaise, 1992</td>
<td>AML</td>
<td>10 Gy in 1 12 Gy in 6 (BID)</td>
<td>5 (median) 8 (median)</td>
</tr>
<tr>
<td>French Blaise, 1995</td>
<td>CML</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td>Seattle Clift, 1994</td>
<td>CML</td>
<td>12 Gy in 6 QD</td>
<td>6-7</td>
</tr>
</tbody>
</table>

*TBI technique and lung blocking not detailed*

Cy: 120 mg/kg over 2 days, Bu: 16mg/kg PO over 4 days
## % Acute Toxicity

<table>
<thead>
<tr>
<th></th>
<th>Nordic n=167</th>
<th>French-AML n=101</th>
<th>French-CML n=120</th>
<th>Seattle n=142</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TBI / Bu</td>
<td>TBI / Bu</td>
<td>TBI / Bu</td>
<td>TBI / Bu</td>
</tr>
<tr>
<td>Pneumonitis</td>
<td>10 /14</td>
<td>10 / 4 ns</td>
<td>22 / 17 ns</td>
<td>--</td>
</tr>
<tr>
<td>VOD Liver</td>
<td>1 /12</td>
<td>4 / 12 ns</td>
<td>7 / 8 ns</td>
<td>--</td>
</tr>
<tr>
<td>Hemorrhagic cystitis</td>
<td>8 / 24</td>
<td>--</td>
<td>9 / 11 ns</td>
<td>--</td>
</tr>
<tr>
<td>Seizures</td>
<td>0 / 6</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Grade 3-4 acute GVHD</td>
<td>4 / 15</td>
<td>34 / 25 ns</td>
<td>--</td>
<td>20 / 14 ns</td>
</tr>
<tr>
<td>Fatal GVHD</td>
<td>2 / 17</td>
<td>--</td>
<td>4 / 5 ns</td>
<td>--</td>
</tr>
<tr>
<td>Transplant related mortality</td>
<td>9 / 28</td>
<td>8 / 27 0.06</td>
<td>29 / 38 ns</td>
<td>--</td>
</tr>
</tbody>
</table>
Initial Outcome

Nordic
Ringden, 1994

Relapse
Survival

French AML
Blaise, 1992

French CML
Blaise, 1995

Seattle
Clift, 1994

Relapse Survival

Initial Outcome

Nordic
Ringden, 1994

Relapse
Survival

French AML
Blaise, 1992

French CML
Blaise, 1995

Seattle
Clift, 1994
Long-term Results -- Pooled

**CML**

- \( n = 316 \)
- Survival: \( p = 0.73 \)
- Disease-free survival: \( p = 0.50 \)

**AML**

- \( n = 172 \)
- Survival: \( p = 0.068 \)
- Disease-free survival: \( p = 0.051 \)

Socie et al Blood 98:3569, 2001
TBI
for
Acute Lymphoblastic Leukemia
Pediatric Blood and Marrow Transplant Consortium

- Randomized 43 high-risk ALL pts.
- Most in CR 2
- median age 8 yrs.
- Allogeneic stem cell transplant
- Etoposide 40 mg/kg, cytoxan 120 mg/kg
  - Busulfan 16 mg/kg OR
  - TBI 1200 cGy 200/fx BID (no tech. Details)
- Median f/u 43 months

Bunin et al Bone Marrow Trans 32:543, 2003
Pediatric Blood and Marrow Transplant Consortium

<table>
<thead>
<tr>
<th></th>
<th>Bu</th>
<th>TBI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td># of relapses</td>
<td>9</td>
<td>7</td>
<td>ns</td>
</tr>
<tr>
<td>% EFS</td>
<td>29</td>
<td>58</td>
<td>0.03</td>
</tr>
<tr>
<td>% Survival</td>
<td>47</td>
<td>67</td>
<td>0.09</td>
</tr>
</tbody>
</table>

Bunin et al. Bone Marrow Trans 32:543, 2003
Nordic Trial

- Included 38 ALL patients randomized
- Bu-Cy vs Cy-TBI (10 Gy x 1 or 12 Gy in 3-7)
  - Leukemia-Free Survival:
    - 28 % with Bu
    - 45 % with TBI (ns)
  - Less Toxicity with TBI

Ringden et al Blood 93:2196, 1999
International Bone Marrow Transplant Registry

- Retrospective analysis of 627 ALL patients
- Bu-Cy vs Cy-TBI as prep for ALLOGENEIC transplant
- No TBI details
- Results:
  - Relapse Free Survival
  - Treatment Related Mortality

Overall survival also improved with TBI

**Better efficacy and lower toxicity with TBI**
TBI Outcome Summary

• Non-myeloablative, low dose TBI has a potential palliative benefit in lymphoid malignancies

• For BMT/SCT preparation: TBI containing regimens offer improved efficacy and toxicity – (especially ALL and AML) compared to chemotherapy only regimens

• Concerns persist for late effects with the use of TBI for childhood leukemia which limits its use
TBI Technical factors:

Fractionation
Institut Gustave Roussy

- Randomized trial 160 pts (ALL, AML, CML, MM, NHL)
- 8 year median f/u
- Allogeneic and Autologous transplants (selection?)
- Cytoxan OR Melphalan (selection?) AND TBI:
- 18 MV, partial lung shielding used, (technique?)

<table>
<thead>
<tr>
<th>STBI</th>
<th>HTBI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 cGy x 1</td>
<td>135 cGy x 11 (BID) = 1485 cGy</td>
</tr>
<tr>
<td>4.5 cGy / min</td>
<td>25 cGy / min</td>
</tr>
<tr>
<td>Lung = 8 Gy</td>
<td>Lung = 9 Gy</td>
</tr>
</tbody>
</table>

Girinsky et al JCO 18: 981, 2000
Institut Gustave Roussy -- Survival

Trend for better survival with fractionation

Girinsky et al JCO 18: 981, 2000
Institut Gustave Roussy -- Toxicity

Pneumonitis

Veno-occlusive disease of liver

Fractionation
Less toxic

Girinsky et al JCO 18: 981, 2000
University of Washington, Seattle

- Randomized trial of 53 AML patients
- Allogeneic BMT with Cytoxan and TBI:
- $^{60}\text{Co}$ (technical details?)

<table>
<thead>
<tr>
<th>Single fraction</th>
<th>Fractionated</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 cGy x 1</td>
<td>200 cGy x 6 (QD)</td>
</tr>
<tr>
<td>8 cGy / min</td>
<td>1200 cGy</td>
</tr>
</tbody>
</table>

Thomas et al IJROBP 8: 817, 1982
Both tolerated well
At initial follow-up only 1 pt in each arm relapsed
But worse transplant-related mortality in the single fraction arm,

**Survival advantage** to fractionated TBI

Thomas *et al* *IJROBP* 8: 817, 1982
TBI Technical Factors:

Dose
University of Washington, Seattle

- Randomized trial of 116 CML patients
- Allogeneic BMT with Cytoxan and TBI:
- \(^{60}\text{Co}\) (technique?)

<table>
<thead>
<tr>
<th>1200 cGy</th>
<th>1575 cGy</th>
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<tbody>
<tr>
<td>200 cGy x 6 (QD)</td>
<td>225 cGy x 7 (QD)</td>
</tr>
<tr>
<td>6-7 cGy / min</td>
<td>6-7 cGy / min</td>
</tr>
</tbody>
</table>

University of Washington, Seattle

- Rate of relapse lower with high dose TBI
- But also higher transplant-related mortality 21% vs 34% (CMV pneumonia/pneumonitis, VOD)
- Therefore no difference in overall survival.

Clift et al Blood  77:1660, 1991
TBI Technical Factors:

Dose rate
French Multi-institutional

- Prospective randomized trial 157 pts comparing high vs low dose rate TBI with Cytoxan
- Allogeneic or autologous BMT

1000 cGy x 1
6MV APPA
Lung 800 cGy

200 cGy x 6 BID
(4hr IFI) 60Co
APPA Lung 900 cGy

<table>
<thead>
<tr>
<th>Dose Rate</th>
<th>High Dose Rate</th>
<th>Low Dose Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1000 cGy</td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>200 cGy</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

Ozsahin et al Cancer 69:2853, 1992
• No difference in:
  – Relapse-free survival
  – Overall survival
  – Graft vs Host disease
  – Pneumonitis

Ozsahin et al Cancer 69:2853, 1992
TBI Technical Factors:

Lung Blocking
Institute Gustave-Roussy

- Randomized trial of lung dose
- 85 patients with AML, ALL, CML, Allo BMT
- Cytoxan and TBI (1000 cGy x1 at 4 cGy/min)
- “Lung dose” randomly assigned to:

600 cGy  OR  800 cGy

Girinsky IJROBP 30:821, 1994
Institute Gustave-Roussy

- Median f/u 24 months
- No difference in risk of lung complications
- Higher relapse in the 6 Gy arm
- Overall survival
  - 59% 8 Gy (ns)
  - 43% 6 Gy

Girinsky IJROBP 30:821, 1994
University of Zagreb

- Randomized trial lung blocking
- 64 patients with AML, ALL, CML
- Allo BMT with Cytoxan and TBI:
  - 400 cGy x 3 over 3 days, $^{60}$Co… (no details!)

Lung Blocking
Lung dose 9 Gy

vs

Lung Blocking
Lung dose 12 Gy

Labar et al/ Bone Marrow Trans 9:343, 1992
University of Zagreb

- No sig. difference in lung complications (but trend to worse pneumonitis without lung blocking)
- No difference in disease relapse.
- Advocate lung shielding

Labar et al/ Bone Marrow Trans 9:343, 1992
TBI technical Factor Summary

- Fractionation associated with less toxicity.
- 1200 cGy in 6 fractions with Dose Rate of 10 cGy/min represents a reasonable standard for myeloablative conditioning.
- Dose escalation (1500 cGy) with standard techniques leads to lower relapse BUT increased toxicity.
- Need for lung blocking is not established in clinical trials, but limiting lung dose to 8-9 Gy is reasonable.
Opposed Laterals

Fig. 1. Treatment geometry in a small [220 cm source-axis distance (SAD)] therapy room. The 87 cm × 87 cm field is rotated so the 123 cm field diagonal coincides with the cephalad-caudal dimension of the patient.
Opposed Laterals
Opposed Lateral Dose Distribution
Compensators used to limit heterogeneity at the head and neck region.

The degree of compensation is based on the ratio of head to waist separations.

Additional compensation for lower extremities is optional.
Opposed Laterals -- Lung Blocking

Transmission block: Lung mean dose 800 cGy (1200 cGy prescription)
Position with port film before each fraction
Often requires larger field size, therefore longer SSD
Can be more difficult to position
Lung blocking mandatory in myeloablative regimens
APPA

Mean lung dose 800-900 cGy
# TBI Dose and Fractionation

<table>
<thead>
<tr>
<th>Dose per Fraction cGy</th>
<th># fx</th>
<th>Days</th>
<th>Total Dose cGy</th>
<th>Approx. Dose Rate cGy/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>200 BID</td>
<td>6</td>
<td>3</td>
<td>1200</td>
<td>10</td>
</tr>
<tr>
<td>165 BID</td>
<td>8</td>
<td>4</td>
<td>1320</td>
<td>10</td>
</tr>
<tr>
<td>175 BID</td>
<td>7</td>
<td>4</td>
<td>1225</td>
<td>10</td>
</tr>
<tr>
<td>120 TID</td>
<td>11</td>
<td>4</td>
<td>1320</td>
<td>10</td>
</tr>
<tr>
<td>400 QD</td>
<td>2</td>
<td>2</td>
<td>800</td>
<td>25</td>
</tr>
<tr>
<td>550 x 1</td>
<td>1</td>
<td>1</td>
<td>550</td>
<td>30</td>
</tr>
<tr>
<td>200 x 1</td>
<td>1</td>
<td>1</td>
<td>200</td>
<td>10</td>
</tr>
</tbody>
</table>
Future Directions:

Intensity Modulated Radiation Therapy Applied to TBI
IMRT Advantages

- Bone marrow dose escalation possible
- With relative sparing of normal critical tissues (lung, liver, kidneys)
- Potential to improve therapeutic ratio
- Facilitate concomitant boosts (cranial)
IMRT Difficulties

• Patient positioning -- entire body, including arms and legs, fingers, toes
• Planning times – contouring!
• Treatment delivery:
  – Times
  – Matching large IMRT fields (VMAT)
  – Table sag
  – Matching to lower extremity fields
• No established dose response or dose constraints on normal tissues
Table II. Median dose in various organs for prescription dose (Rx) of 6 Gy.

<table>
<thead>
<tr>
<th>Anatomy</th>
<th>TMI dose</th>
<th>% dose reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>pTV (upper body)</td>
<td>6.14</td>
<td>0.29</td>
</tr>
<tr>
<td>pTV (lower body)</td>
<td>6.00</td>
<td>0.03</td>
</tr>
<tr>
<td>lungs</td>
<td>3.37</td>
<td>1.26</td>
</tr>
<tr>
<td>eyes</td>
<td>3.67</td>
<td>1.27</td>
</tr>
<tr>
<td>lens</td>
<td>2.01</td>
<td>0.59</td>
</tr>
<tr>
<td>right kidneys</td>
<td>2.32</td>
<td>1.56</td>
</tr>
<tr>
<td>left kidney</td>
<td>2.48</td>
<td>1.48</td>
</tr>
<tr>
<td>liver</td>
<td>4.17</td>
<td>1.22</td>
</tr>
<tr>
<td>heart</td>
<td>4.21</td>
<td>1.25</td>
</tr>
<tr>
<td>scrotum</td>
<td>0.71</td>
<td>0.15</td>
</tr>
</tbody>
</table>

Linear Accelerator

Comparison of median doses (Gy) to organs at risk for linac-based TMI and conventional TBI\textsuperscript{11}.

<table>
<thead>
<tr>
<th>Organ</th>
<th>TMI</th>
<th>TBI</th>
<th>Ratio of TBI/TMI Median Doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>7.0</td>
<td>8.8</td>
<td>1.3</td>
</tr>
<tr>
<td>Liver</td>
<td>6.5</td>
<td>12.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Kidneys</td>
<td>6.8</td>
<td>12.2</td>
<td>1.8</td>
</tr>
<tr>
<td>Heart</td>
<td>7.1</td>
<td>12.1</td>
<td>1.7</td>
</tr>
<tr>
<td>Lenses</td>
<td>2.5</td>
<td>11.3</td>
<td>4.5</td>
</tr>
<tr>
<td>Eyes</td>
<td>3.0</td>
<td>11.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Brain</td>
<td>7.3</td>
<td>12</td>
<td>1.6</td>
</tr>
</tbody>
</table>

“Targeted Marrow Irradiation” Clinical Trial

<table>
<thead>
<tr>
<th>STUDY NUMBER:</th>
<th>CASE9Z13</th>
</tr>
</thead>
<tbody>
<tr>
<td>STUDY TITLE:</td>
<td>Phase I Trial of Escalated Doses of Targeted Marrow Irradiation (TMI) Combined with Fludarabine and Busulfan as conditioning regimen for allogeneic hematopoietic progenitor cell transplantation.</td>
</tr>
</tbody>
</table>
• Use Volumetric Modulated Arc Therapy (VMAT) with multiple arcs
• Targeted marrow dose to be escalated from 6 Gy to 18 Gy. Delivered BID over 2-4 days with 6 hour interfraction interval.
• Done in addition to chemotherapy preparative regimen (Fludarabine and Busulfan):
Contouring

Target is Bones and spleen

7mm expansion to PTV

Courtesy Gisele Pereira
Volumetric Modulated Arc Therapy (VMAT)
Targeted Marrow Irradiation (TMI) with 3 Arcs

Lower extremities treated with opposed lateral beams at extended SSD matched to VMAT treatment volume

Courtesy Gisele Pereira
Volumetric Modulated Arc Therapy (VMAT) Targeted Marrow Irradiation (TMI) with 3 Arcs

Courtesy Gisele Pereira and Wayne Swanson
TMI Dose Volume Histogram
## TMI Dose Escalation

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>Day -10 dose (Gy)</th>
<th>Day -9 dose (Gy)</th>
<th>Day -8 dose (Gy)</th>
<th>Day -7 dose (Gy)</th>
<th>Total Dose (Gy)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AM dose</td>
<td>1.5</td>
<td>1.5</td>
<td>--</td>
<td>--</td>
<td>6</td>
</tr>
<tr>
<td>PM dose</td>
<td>1.5</td>
<td>1.5</td>
<td>--</td>
<td>--</td>
<td>6</td>
</tr>
<tr>
<td><strong>Level 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AM dose</td>
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<td>1.5</td>
<td>1.5</td>
<td>--</td>
<td>9</td>
</tr>
<tr>
<td>PM dose</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>--</td>
<td>9</td>
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<tr>
<td><strong>Level 3</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>AM dose</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>12</td>
</tr>
<tr>
<td>PM dose</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>1.5</td>
<td>12</td>
</tr>
<tr>
<td><strong>Level 4</strong></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AM dose</td>
<td>1.625</td>
<td>1.625</td>
<td>1.625</td>
<td>1.625</td>
<td>13</td>
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<tr>
<td>PM dose</td>
<td>1.625</td>
<td>1.625</td>
<td>1.625</td>
<td>1.625</td>
<td>13</td>
</tr>
<tr>
<td><strong>Level 5</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>AM dose</td>
<td>1.75</td>
<td>1.75</td>
<td>1.75</td>
<td>1.75</td>
<td>14</td>
</tr>
<tr>
<td>PM dose</td>
<td>1.75</td>
<td>1.75</td>
<td>1.75</td>
<td>1.75</td>
<td>14</td>
</tr>
<tr>
<td><strong>Level 6</strong></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>AM dose</td>
<td>1.875</td>
<td>1.875</td>
<td>1.875</td>
<td>1.875</td>
<td>15</td>
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Obrigado