Thinking outside the box: Chemotherapy dose adjustment for obese patients undergoing hematopoietic stem cell transplantation

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Introduction
For many years we were used to adjust chemotherapy dose for obese patients with little evidence of the necessity and consequences of that.

We put all patients in the “thin patient box” according to our “ideal weight”, no matter how much obese they were.

Lately, we realized that we should think outside the box, and consider adjustment more thoroughly.

THINKING OUTSIDE THE BOX: Should dose of conditioning chemotherapy be adjusted in obese patients?
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- In this session I will introduce our current knowledge of obesity and chemotherapy, in order to achieve a better answer to this question of adjustment chemotherapy dose.
Introduction: Obesity and cancer

- The incidence of obesity has substantially increased in recent years.
- Among cancer patients, obesity is associated with a greater overall and cancer-specific mortality.
- Obese patients are more likely to suffer from co-morbidities such as cardiovascular disease and diabetes, which might affect significantly complications during chemotherapy and thus increase mortality.
Epidemiologic studies have shown that obese individuals have a greater risk for developing cancer in general and leukemia in particular.

Until recently little research has been directed toward understanding how high fat diet and adiposity impact the function of hematopoietic stem cells and affect the immune system.
Using a murine model Adler et al (PLoS One 2014) investigated the effects of a high fat diet on hematopoiesis. They found a sustained loss of B and T lymphocytes populations, probably secondary to reduced IL-7 secretion that is necessary to support the development of lymphocytes and to the commitment of B cells.

Of course additional studies are needed to understand this complicated system, nonetheless these preliminary data support the marrow as a dynamic organ whose function is significantly influenced by nutritional factors.
Pharmacokinetics of drugs including chemotherapy is different in obese patients due to alteration in renal and hepatic clearance, increased volume of distribution of lipophilic drugs and increased protein binding.

Thus, appropriate chemotherapy dosing for obese patients with malignant diseases is a significant challenge.
Limiting chemotherapy doses in overweight and obese patients may negatively influence the outcomes in these patients and on the other hand overdosing might increase toxicity
Introduction: Determining chemotherapy dose in obese patients

- The current practice for determining chemotherapy dose uses body surface area (BSA) based on animal and human studies performed decades ago.
- Some chemotherapeutic drug dose is based on body weight.
- In either case, weight for calculation should be determined in obese patients.
The 2012 panel review by the ASCO published clinical practice guidelines for *conventional* chemotherapy dosing for obese patients with cancer indicating that up to 40% of obese patients received reduced chemotherapy doses that are not based on actual body weight (ABW).

Many oncologists continue to use either ideal body weight or adjusted ideal body weight or to cap the BSA at, for example, 2.0 m² rather than use actual body weight to calculate BSA.

This is mainly due to traditional concerns about toxicity or overdosing in obese patients if the ABW was to be used.
The ASCO panel recommended that full weight-based cytotoxic chemotherapy doses must be used to treat obese patients with cancer because there is no evidence that short or long-term toxicity is increased among obese patients receiving full weight-based doses.

Of note, most data indicated that myelosuppression is similar or less pronounced among obese compared to the non-obese.
The question of dose adjustments is even more complicated in high dose conditioning chemotherapy.

There is a paucity of information addressing the pharmacokinetics of high dose chemotherapy in obese patients undergoing HSCT.

The kinetics is more complicated than in standard dose chemotherapy because of metabolizing enzyme saturation, depletion of conjugating substrate and significant protein binding and changes in volume distribution.
There is also limited clinical information.

A relatively small international survey of drug dosing schemes among transplant centers revealed that there is no consensus regarding appropriate dose adjustment for obese patients (Grigg, Leukemia and Lymphoma, 1997).

52 BMT centers were sent a questionnaire for details of dosing for busulfan (Bu), cyclophosphamide (Cy), cyclosporin A and methotrexate.

33 centers were evaluable.
Introduction: HD-Chemotherapy and obesity

- No single method was used in more than 30% of transplant centers:
  - 24% and 30% of centers surveyed used actual weight without modification for Bu and Cy respectively,
  - 15% and 12% used ideal weight for Bu and Cy respectively.
  - The remainder used various dose adjustment schemes.
Moreover, there is limited data on outcome in obese versus non-obese patients.

Some reports suggested a higher treatment-related mortality (TRM) while others showed only higher relapse rates.

No optimal approach to adjustment is clear from the literature, variable dosing schemes and consequent under- or overdosing is used.

In addition different adjustment is probably needed for different drugs.
In review of relevant studies in autologous transplantation we found different results regarding TRM, relapse and OS.

Moreover, some of the obese patients were overdosed while other were under-dosed so analysis of the data is problematic.

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>N (obese/total)</th>
<th>Dose adjust?</th>
<th>TRM % (obese)</th>
<th>5y EFS % (obese/nonobese)</th>
<th>5y OS % (obese/nonobese)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navarro</td>
<td>AML</td>
<td>13/32</td>
<td>Yes</td>
<td>0</td>
<td>51 vs 57 (P=NS)</td>
<td>68 vs 68 (P=NS)</td>
</tr>
<tr>
<td>Meloni</td>
<td>AML</td>
<td>9/54</td>
<td>No</td>
<td>33</td>
<td>22 vs 53</td>
<td>22 vs 55</td>
</tr>
<tr>
<td>Tarella</td>
<td>NHL</td>
<td>28/121</td>
<td>6/28</td>
<td>2</td>
<td>23 vs 55</td>
<td>38 vs 65</td>
</tr>
<tr>
<td>Coghlin</td>
<td>various</td>
<td>104/473</td>
<td>Yes</td>
<td>33</td>
<td>36 vs 47 (P=NS)</td>
<td>NR</td>
</tr>
</tbody>
</table>
In the setting of allogeneic SCT, data is from retrospective analysis of small numbers of obese patients in heterogenic groups.

Results are conflicting.

<table>
<thead>
<tr>
<th>Study</th>
<th>Disease</th>
<th>Donor type</th>
<th>N (obese/total)</th>
<th>Dose adjust?</th>
<th>TRM % (obese)</th>
<th>OS % (obese/nonobese)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fleming</td>
<td>Various</td>
<td>Various</td>
<td>76/242</td>
<td>NR</td>
<td>63</td>
<td>16 vs 30</td>
</tr>
<tr>
<td>Deeg</td>
<td>Various</td>
<td>Auto &amp; Allo</td>
<td>250/1475</td>
<td>No</td>
<td>42</td>
<td>NR vs 62 est (P=NS)</td>
</tr>
<tr>
<td>Hansen</td>
<td>CML</td>
<td>Unrelated</td>
<td>44/196</td>
<td>No (TBI based)</td>
<td>NR</td>
<td>NR vs 74</td>
</tr>
</tbody>
</table>
Data from EBMT survey:
Methods
The ALWP of the EBMT designed an electronic survey for assessing current practice of dose adjustment of chemotherapy in obese patients undergoing HSCT.

This was a prospective survey that was carried out between February 2013 and July 2013.

The questionnaire included 27 items regarding definition of obesity and various aspects of conditioning chemotherapy dose adjustment.

EBMT transplant centers were invited to participate, among which 56 centers from 27 countries responded and filled the online survey.
Definitions for the Survey

- **BMI** – Body Mass Index
  - BMI (kg/m²) = body weight / height²
- **BSA** – Body Surface Area
- **ABW** – Actual Body Weight
- **IBW** – Ideal Body Weight
  - IBW (kg, men) = 50 + 0.91 x (height (cm) – 152)
  - IBW (kg, woman) = 45 + 0.91 x (height (cm) – 152)
- **AIBW** – Adjusted Ideal Body Weight
  - AIBW-25 (kg) = IBW + 0.25 x (ABW – IBW)
  - AIBW-40 (kg) = IBW + 0.40 x (ABW – IBW)
- **MBW** – Mean Body Weight
  - MBW (kg) = (ABW + IBW) / 2
• Weight which is considered for adjustment – optional values:
  – According to BMI:
    • Overweight = BMI > 25 kg/m²
    • Obese = BMI > 30 kg/m²
    • Morbid obese = BMI > 40 kg/m²
  – According to IBW:
    • ABW > 1.2 x IBW
    • ABW > 1.5 x IBW
Example

• Which method do you use for determining body weight for dose adjustment?
  o We use only ABW
  o IBW
  o AIBW-25
  o AIBW-40
  o MBW
  o Other - please specify ____________________

Comment

Multiple choice and possibility for other answer and comments
Data from EBMT survey:
Results
EBMT survey: Results

- 45 (80.5%) centers declared that they adjust chemotherapy dose for obese patients.
- 11 (19.5%) centers do not adjust chemotherapy dose for obese patients.

**Dose adjustment for chemotherapy in obese patients**

- Yes: 80%
- No: 20%
Results: Definition of Obesity

- Among centers which routinely applied dose adjustment, most used BMI as the parameter for defining obesity (n=28, 62%)
- Other centers used percentage of ABW over the IBW (n=11, 24.5%), both BMI and ABW (n=3, 6.7%) or other parameters (n=3, 6.7%)
In most of the centers that used BMI for dose adjustment, BMI > 30 kg/m² was defined as the cut-off value for definition of obesity.

Only one center used morbid obesity (BMI > 40 kg/m²), and the remainder used other cut-off values.

Among 11 centers that used ABW, 9 used ABW more than 120% of IBW for adjustment and the other used ABW more than 140% of IBW.
Results: Determining the weight for chemotherapy

- The method for determining the weight for chemotherapy calculation was:
  - ABW in 16 centers,
  - IBW in 10 centers,
  - IBW+25% of difference between IBW and ABW (IBW + 0.25 \times (ABW - IBW)) in 16 centers,
  - IBW+40% of difference between IBW and ABW (IBW + 0.4 \times (ABW - IBW)) in 4 centers
  - other methods in the rest (n=2)
Results: Capping

- Among centers that used dose adjustment, 44% also capped the dose at 2m$^2$ for chemotherapy dose based on BSA while 56% did not cap.

- Most of the centers (9 out of 11) that did not adjust dose for weight also did not cap BSA at 2m$^2$.

- 12 centers declared they capped BSA at values higher than 2m$^2$.
Results: Example

- height - 170 cm
- weight - 125 kg
- BMI - above 30 (43.3) kg/m²
- IBW – 65 kg
- BSA for ABW - 2.3 m²
- BSA for IBW - 1.8 m²

- For standard fludarabine-busulfan conditioning we get a difference of 27% in fludarabine dose which is based on BSA and 92% difference in busulfan dose which is based on weight.
- With some method of correction and capping at 2 m² we can get doses in between these 2 extreme values.
For Bu dosage, only 7 centers monitored routinely PK

Eleven centers used IBW for calculation of Bu dose, 17 centers used ABW and 18 centers corrected weight according to percentage over IBW

In most of transplant centers (86%), formulation of Bu dose is based on weight and only the minority used BSA
Results: Chemotherapy dose calculation

- For other cytotoxic drugs used as part of conditioning regimens, the majority of centers (n=38) used the same method for weight adjustment for the various drugs.
- No center used IBW for dose calculation for other cytotoxic drugs than Bu.
- The most commonly used adjustment methods were ABW in 15 centers, AIBW-25 in 13 centers and AIBW-40 in 3 centers.
Results: MAC vs NMA/RIC

- 36 centers declared they used the same approach to dose adjustment in myeloablative (MAC) versus reduced intensity (RIC) or non myeloablative (NMA) regimens

- 8 centers declared they did a smaller dose reduction for RIC or NMA regimens
Results: Calculation for other drugs

- For drugs used for graft versus host disease (GVHD) prophylaxis and treatment, and for supportive care most of the centers used ABW for dose calculation without a specific adjustment.
Data from EBMT survey:
Discussion
This EBMT survey reveal large diversity among transplant centers regarding dose adjustment practice for high dose conditioning chemotherapy in obese patients.

Most of the centers use dose adjustment for chemotherapy calculation, while BMI > 30kg/m² is used most commonly as the cut-off value.

There was no common method for adjustment and weight calculation that varied from IBW, through corrected IBW (e.g. IBW+25% of difference between actual and ideal weight), to actual weight.
An interesting fact is that about half of centers that used dose adjustment also capped BSA at 2m², while capping was uncommon in the centers that did not adjust doses. Thus, the range of the final dose might become even wider.

Even for busulfan where dose is traditionally calculated according to IBW, the diversity applied to obese patients was striking.
In view of these findings, I would like to finish with a recent ASBMT position statement on conditioning chemotherapy dose adjustment in obese patients (Bupalo, BBMT 2014).

The ASBMT practice guideline committee reviewed the literature on the dosing of agents used for conditioning regimens with specific focus on the obese patient population.
The review found that dose adjustment for obesity have been based empirically or extrapolated from published data in the non-transplantation patient population.

As a result, the committee determined that clear standards or dosing guidelines are unable to be made for the obese population.

The committee provides a current published literature review to serve as a platform for conditioning agent dose selection in the setting of obesity.

Given the limitations of existing literature, the committee suggests consensus recommendations.
American Society for BMT (ASBMT) - position statement

- **Summary of recommendation for common agents (adults):**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Suggested Dosing</th>
</tr>
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<tbody>
<tr>
<td>Busulfan</td>
<td>Dose on AIBW25 receiving per kg dosing or BSA based on TBW for $m^2$ dosing, recommended PK targeting.</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>For Cy120 dosing can be either IBW or TBW unless $&gt;120%$ IBW then dose based on AIBW25.</td>
</tr>
<tr>
<td>Fludarabine</td>
<td>Dose on BSA based on TBW.</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Dose on BSA based on TBW.</td>
</tr>
<tr>
<td>Carmustine</td>
<td>Dose on BSA based on TBW unless $&gt;120%$ IBW then dose on BSA based on AIBW25.</td>
</tr>
<tr>
<td>Cytarabine</td>
<td>Dose on BSA based on TBW.</td>
</tr>
<tr>
<td>Etoposide</td>
<td>Dose on AIBW25 for mg/kg dosing and BSA based on TBW for BSA based dosing.</td>
</tr>
<tr>
<td>ATG</td>
<td>Dose on mg/kg based on TBW.</td>
</tr>
</tbody>
</table>
Conclusions

- In the field of high dose chemotherapy we have little evidence to analyze in order to suggest practice guidelines.

- Analysis based on this scanty data is challenging because of differences in definitions of obesity and adjustments of weight, heterogeneous patient population and diseases, heterogeneous conditioning and graft sources.
Standardization of chemotherapy dose is very important to the individual patient as well as to the general population of patients.

To the individual patients we must have standard schemes to define which is the dose that will be enough for efficacy but not too much to avoid severe toxicity.

For the general population of patients we must have standards for comparisons between different conditioning regimens, in different transplant centers.
As long as obesity is defined and treated so differently we could not compare studies and improve conditioning regimens accordingly.

Standard of care nowadays is a hot topic in many fields of medicine and influence health care policy, so transplant organizations should promote this topic.
Our next steps:

- To analyze outcomes of transplantation among obese patients according to dose adjustment practice and actual chemotherapy dose that is given.

- According to the results and recent American guidelines we should formulate a methodology for future prospective studies.
Thank you!

"No, it's not water. You seem to be retaining food."