Busulphan-melphalan as a myeloablative therapy (MAT) for high-risk neuroblastoma: Results from the HR-NBL1/SIOPEN trial

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**Background**

- **Neuroblastoma** is a cancer of the sympathetic nervous system and is comprised of a spectrum of tumors arising from the primitive ganglion cells.
- It is the most common extracranial solid malignancy of childhood and the most common malignancy of infants.
- High-risk features include older age at diagnosis (> 18 months), wide spread dissemination, MYCN gene amplification, poor or undifferentiated tumor, and diploidy.
- Treatment for high-risk patients typically includes aggressive induction chemotherapy, maximal surgical resection, myeloablative therapy (MAT), bone marrow transplant, and consolidative radiation therapy to the primary tumor site and sites of residual disease.
- Long-term survival is poor for high-risk patients in spite of multimodality treatment.
- The HR-NBL1 trial, described here, was developed in order to compare two MAT regimens, with a primary aim of demonstrating superiority in event free survival (EFS).

**Methods**

- 1,577 patients with high-risk neuroblastoma were randomized on this study between June 2002 to September 2010
- Eligibility criteria: INSS stage IV neuroblastoma and age greater than 1 year, or INSS stage II-III with MYCN amplification at any age
- Study scheme:
All patients were treated with rapid COJEC Induction therapy (cisplatin, vincristine, carboplatin, etoposide, and cyclophosphamide given in a rapid delivery schedule; JCO 2010) +/- TVD (topotecan, vincristine, doxorubicin; Cancer 2003)

Patient were then randomized to one of two MAT regimens:

BuMel

- Busulfan: oral busulfan till 2006, 4x150mg/m2 in 4 equal doses, then after 2006 intravenous use according to body weight
- Melphalan: 140mg/m2/day

CEM

- Carboplatin: continuous infusion (4 x AUC 4.1mg/ml.min/day)
- Etoposide: continuous infusion [4 x 338mg/m2day or 4x200mg/m2/day]

All patients received maintenance phase cisplatin

590 patients were randomized in total à 296 to the BuMel arm and 302 to the CEM arm.

Median follow-up was 3.5 years.

Anticipated 2-year EFS was 55% in the BuMel arm, compared to 45% in the CEM arm. The study was powered to detect a 10% difference in 2-year EFS.

Results

The majority of patients were male (n=347) and with stage IV disease (n=494).

Median age at randomization was 3 years.

An intent-to-treat analysis was conducted, and showed a significant difference in EFS favoring the BuMel regimen as compared to the CEM regimen as below:

<table>
<thead>
<tr>
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<th>BuMel</th>
<th>CEM</th>
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<tbody>
<tr>
<td>3-yr EFS*</td>
<td>49%</td>
<td>33%</td>
</tr>
<tr>
<td>3-yr OS*</td>
<td>60%</td>
<td>48%</td>
</tr>
<tr>
<td>Progression/relapse*</td>
<td>48%</td>
<td>60%</td>
</tr>
<tr>
<td>3-yr EFS for stage IV disease*</td>
<td>43%</td>
<td>29%</td>
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* Statistically significant

Differences in EFS and OS were seen in the period prior to 2006 (oral busulfan) as well as after 2006 (IV busulfan)

Toxicity:
The rate of ICU admissions and toxic deaths was below 10%, but was significantly higher for the CEM arm. The incidence of veno-occlusive disease (VOD) secondary to BuMel was 18%. The treatment-related mortality rate was not different between the two arms, 3% BuMel vs. 5% CEM.

On multivariate analysis, predictors for longer EFS were localized disease and BuMel therapy. Age was not a significant predictor of an event. Based on results obtained at the time of preliminary analysis, the study was closed early due to the superiority of BuMel.

Authors' Conclusions

BuMel was demonstrated to be superior to CEM and is therefore recommended by the authors as standard MAT for high-risk neuroblastoma. This effect is likely mediated through a lower relapse rate with BuMel. The superiority of BuMel was accentuated in patients with residual disease post-induction. The authors attribute this to the activity of the drug against resting tumor cells. Although toxicities are seen with BuMel, the authors report that the VOD rate is acceptable.

Implications

In spite of aggressive treatment, high-risk neuroblastoma has a poor prognosis. Deaths from neuroblastoma unfortunately account for 15% of childhood cancer mortality. Data from randomized trials have changed the management of neuroblastoma and improved outcomes. Three randomized trials have demonstrated that post-induction MAT and auto stem cell transplant improve EFS. Interestingly, the results of the CEM arm on this study underperformed as compared to other randomized trial data. 3-yr EFS in CCG 3891 and A3973/ANBL0032 was in the range of 46-64% depending on administration of immunotherapy. The 3-year EFS of 33% is also lower than anticipated by the authors. Further investigation to elucidate the underperformance of the control arm is necessary. Perhaps the low EFS is due to differences in the induction regimen (N6 vs. rapid COJEC), dose intensity, and cumulative dose. Additionally, the COG study included more Stage III, MYCN non-amplified patients, patients with a higher burden of disease, and more patients who received immunotherapy as compared to SIOPEN. Indeed, these results may not apply to the patient population studied in the COG trials. Generalizability of the data must be examined, and the BuMel regimen should be validated in the cohort studied in the COG trials before it is adopted as the standard of care. Additionally, it should be noted that 57% of patients went off protocol prior to consolidation, and were therefore not randomized, due to inadequate disease response to induction therapy.

In summary, this important trial confirms the importance of MAT in the treatment of high-risk neuroblastoma. In the patient population studied, BuMel was superior to CEM. However, these results may not apply to patients treated with a difference induction regimen, dose intensity, total dose, or use of BuMel with other biologic or immunotherapy agents. Additionally, the 18% incidence of VOD described as part of this study in patients receiving BuMel is important, and should be taken into account during determination of future regimens.

Future trials must address the need for improved induction agents and also advancement of post-consolidation biologic agents and immunotherapy.