HEMATOLOGY

Treating advanced frontline Hodgkin Lymphoma

CARE™ GUIDANCE 2022

VERSION 1.0

CONTENT AS OF DECEMBER 2022

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Treating advanced frontline HL

CARE™ Hematology Faculty Guidance V1.0 - CONTENT AS OF DECEMBER 2022

BACKGROUND

Guidance was developed by CARE™ Hematology Faculty working group that was held at ASH, December 8, 2022, with follow-up review by faculty.

CARE™ Faculty Members who have contributed to this Guidance:

Faculty lead: Dr. John Kuruvilla, PMCC
Participants: Dr. Peter Anglin, Southlake Regional Cancer Centre; Rob Laister PhD, PMCC, with additional review and commentary by Dr. Isabelle Fleury, HMR

ECHELON 1 trial establishes BV-AVD as preferred for stage III/IV HL In advanced frontline HL.

- Longer term follow-up of Echelon-1 (Ansell NEJM 2022) now demonstrates an OS benefit along with continued PFS benefit with long term follow-up
    - This benefit is seen in the total population and subgroup analyses do not clearly demonstrate lack of benefit in stage III or older cHL

- In patients that were considered for an ABVD-based approached, **BV-AVD should be considered as the default**
- For patients with concerns about toxicity with BV-AVD (older, pre-existing comorbidity), alternative regimens (ABVD or other) should be used
- **Toxicity management with BV-AVD** (neutropenia and neuropathy) should be in line with practice in other curable lymphomas

CARE™ faculty believe in funding for stage III despite prior Health Canada guidance.

Other considerations

Pathology Review

- Ensure a confident diagnosis of classical Hodgkin Lymphoma (cHL) with appropriate pathology review as needed given the increasing use of needle core biopsies for diagnosis
- Routine disease staging should include PET-CT in all patients (Lugano Classification, JCO 2014)

Prognostic Factor Assessment

- Routine prognostic factor assessment (IPS, Hasencleaver NEJM 1998) should be performed in every patient and can help to inform select specific treatment choice

Considerations – younger/fit and for patients that do not achieve CR or relapse

- Patients (typically younger, fit) can still be considered for escBEACOPP-based approaches in the setting of high-risk disease (based on IPS) or other specific considerations for individual patients (Borchmann Lancet 2017; Casasnovas Lancet Oncol 2019)

Supporting Discussion from working group meeting (Dec 8, New Orleans) that informs Guidance

Questions were posed to participants by faculty lead, who also participated in discussion.

4 key areas of focus with additional discussion on personalizing front-line therapy for cHL:

- What is the right population for BV-AVD in the SOC setting?
- How do you manage the patient on BV-AVD?
- Additional insights from ECHELON 1 study
- Considerations and challenges with BV-AVD

Points that follow are a summary of discussion / consolidation of notes, with review by participating faculty

1. **What is the right population for BV-AVD in the SOC setting?**

   Assessment

   Initial assessment must include clarifying histology, staging extent of disease (PET / CT), and assessing performance status / comorbidities of patient. In addition, assessing the International Prognostic Score (IPS) based on 7 factors (age, stage, gender, serum albumin, hemoglobin, white cell count and lymphocyte count) will place the patient into one of six prognostic groups with quite variable rates of progression free survival.

   Younger versus older

   - *Median age of trial was 36 years for Echelon-1*
   - *Appropriate for majority of patients < 60 years*
   - *> 60 years applicability must be individualized taking into account patient PFS, comorbidities, and goals*
   - *Less pulmonary toxicity (allows avoidance of bleomycin) weighed against increased neutropenia and peripheral neuropathy (cf ABVD)*

   High risk disease by IPS

   - *Younger patients with high-risk disease (IPS > 3) may be considered for BEACOPP benefit over time*
     - *Greatest potential benefit of esc BEACOPP is seen for IPS> 3*
   - *4-6 cycles of esc BEACOPP is as efficacious and less toxic than 8 cycles of esc BEACOPP and is superior to standard (baseline) BEACOPP*
     - *Only consider in patients < 60 years*
     - *Higher rates of secondary malignancies, bone marrow suppression and sterility (cf ABVD)*
     - *Provides superior PFS at 5 years and may result in improved overall survival (OS) vs ABVD*
       - *Cardiac deaths and second malignancies may compromise OS*
   - *Alternative strategy is to consider PET-adapted therapy in this population starting with 2 cycles esc BEACOPP and if PET2 favourable (Deauville 1-3) consider 2 further cycles and stop (HD-18) or de-escalate to ABVD for 4 further cycles (AHL-2011)*
   - *It should be noted that BV-AVD on Echelon-1 trial demonstrated increased benefit cf ABVD in the higher risk IPS group (>3)*

   Are there specific patients that should get escBEACOPP-based approaches

   See above

   Are there specific patients that should not get escBEACOPP or BV-AVD?

   - *Older patients (> 60 years) therapies need to be individualized for patient*
   - *Risk of relapse vs toxicity must be weighed with each patient*
     - *Access to optimal salvage regimens may influence acceptance of increased toxicity with upfront therapy*

2. How do you manage the patient on BV-AVD?

Peripheral neuropathy

- *Primarily sensory neuropathy – common on BV-AVD*
- *Assess each cycle for neuropathy with specific questions*
- *Standards for dose reduction as per trials and monograph with progressive dose reductions and holding BV as increased severity and/or motor compromise*
- *Can insert standard dose reduction chart if needed…*

Growth factor support (timing, days)

- *GCSF used as primary prophylaxis given higher incidence of neutropenia and febrile neutropenia CF ABVD*
- *Start G-CSF with C1 usually administered Day 2-3 with usual course of short-acting agents starting at 7 days. Can be adjusted going forward*
- *Alternatively, may use long-acting GCSF preparations*

Fertility preservation?

- *No difference seen in pregnancy rates when compared with ABVD population however not formally assessed in Echelon-1*
- *Encourage sperm / ovarian banking in all patient considering having children*

Role of interim PET scan?

- *We favour PET2 for prognosis*
- *Data on benefits of dose escalation to escBEACOPP if PET2+ after BV-AVD not known*

3. Additional insights from ECHELON 1 study

- *More toxic than ABVD or PET adapted ABVD to AVD (RATHL)*
- *More neutropenia, more neuropathy, < lung toxicity, needs GCSF*
- *Less toxic than escBEACOPP*

How does PFS in ECHELON 1 really compare?

- *Consider ASH 2022 RATHL presentation*
- *Remember this starts with ABVD and the goes to AVD or escBEACOPP after PET2*
    - *Following a negative PET2, 933 pts were randomised to continue ABVD or AVD. The -1.3% difference in 3yr PFS (95% CI -4.7 to 3.8) remains within the predefined non-inferiority margin of 5%. PFS at 7 years for ABVD was 81% (95% CI 76.9 - 84.4), and for AVD 79.2% (95% CI 75.1 - 82.8), HR: 1.10 (95%CI 0.82 - 1.47) (Figure). Subgroup analyses by stage, International Prognostic Score, presence of bulky disease and B-symptoms did not indicate significant differences in PFS by treatment arm. OS in the PET-negative group was 93.3% at 7 years (95% CI 91.3 - 94.9) with no significant difference between the arms (Figure). Among 172 pts with a positive PET2, 7 year PFS was 65.9% (95% CI 58.1 - 72.6) and 7 year OS 83.2% (95% CI 76.2 - 88.3).*

Fertility and second malignancy data

- *Data from Echelon-1 does not look different than ABVD – no major signals*

4. **Considerations and challenges with BV-AVD**
    - *OS is still OS - if this was a patient you planned to start on ABVD - why not use this?*
    - *BV-AVD is toxic – more so than ABVD*
    - *Peripheral neuropathy (exchanged for pulmonary toxicity)*
    - *Need for growth factor*
    - *Cost*

<u>What to do with >60: other options currently considered</u>

- *ABVD with dose reductions*
- *Most common option in Canada– familiar to clinicians*
    - *Consider omission of bleo*
        - *> 80 yrs ,very frail*
        - *Significant lung disease, active smokers*
        - *CrCl < 10 ml/min*
    - *CHOP rarely*
    - *Single agent BV – rarely used in this indication in Canada*
        - *Sequential BV and then AVD – clinical trial reports (Phase 2) – again rarely used in Canada*

- *Summary/ Context to the above points. Ex. Toxicity is relative. BV-AVD has survival advantage. Dose reduce.*

<u>Use of interim-PET with BV-AVD</u>

Are there qtns or info to share around the use of interim-PET?

- *Trials with BV incorporate interim PET (PET2)*
    - *Predictive of outcome as per ABVD and other regimens*
    - *In future may predict need for consolidation / additional therapy vs less*

<u>Needs and information for community of practice</u>

- *National / Local KOLs to speak of practicalities of delivering BV-AVD*
- *Use of GCSF, neuropathy, dose reductions*
- *We should still do PET2?*

<u>Additional Discussion - Personalizing front-line therapy for cHL</u>

- Can we identify who needs front-line BV-AVD or other?
    - *9p24.1 amplification*
        - *Presently research question and not used routinely in clinic*
        - *Will need maturation of prospective clinical trials for this*

    - *Should checkpoint inhibitors be used in the front-line setting?*
        - *Trials are maturing*
        - *Data will need to move the needle on OS or significant PFS for $ to allow*

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