Optimization of the first line treatment in classical Hodgkin's lymphoma

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Take Home Messages
- Decrease the use of radiation therapy,
- ABVD gold standard in early stages,
- 4 courses of escalated BEACOPP may be sufficient in advanced stages,
- Brentuximab vedotin and nivolumab or Pembrolizumab may be incorporated in first-line treatment in the future.

Optimization of the first line treatment in classical Hodgkin's lymphoma (cHL)

cHL treated with chemotherapy has produced high survival rates and recent strategies aimed to diminish the long-term side effects. A series of randomized trials has confirmed that doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD), first described more than 40 years ago, yields cure rates of 70 to 80% and remains the standard chemotherapy. In moving toward the goal of maximizing cure while minimizing toxic effects, greater individualization of therapy is appealing. Positron-emission tomography (PET) can be used to predict the prognosis in cHL, with a high negative predictive value associated with early metabolic response (Table 1).

Early stages

Therefore, this technique is useful in guiding a response-adapted approach in early-stage cHL, whereby patients who have positive PET findings after chemotherapy receive radiotherapy but patients with early (2 cycles) negative PET findings undergo no further treatment. The late toxic effects of radiotherapy are avoided in patients cured by chemotherapy, and long-term overall survival may be improved. This has been confirmed by two large randomized study with 91% progression free survival in the favorable group (three ABVD courses) and 89.6% in the unfavorable group (six ABVD courses) without radiation therapy. These results are somewhat contradictory because the first study defends the radiotherapy omission while the second failed to show non-inferiority of the omission of radiotherapy in the early-PET negative patients. From a clinical point of view both these results confirm the best outcome for a combined modality which remains a standard of care. But for the youngest patients with unfavorable stage II disease and extended lymph-node involvement or bulky disease the omission of radiotherapy may be a good opportunity to avoid long-term toxicity of radiotherapy.

Advanced stages

Since 2003, it was nicely shown that stage III/IV cHL may be treated with 6 courses of MOPP/ABV (mechlorethamine, oncovin, prednisone, procarbazine, doxorubicin, bleomycin, vinblastine) without radiotherapy if a complete remission is achieved at 4 cycles, this strategy decreases the risk of second solid cancers from the use of radiation therapy. ABVD was shown superior to MOP/ABV for toxicity (mostly infertility and second cancer) but it should be improved. This is possible with escalated therapy with bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (escBEACOPP), with higher-than-standard doses of etoposide, doxorubicin, and cyclophosphamide. This escalated regimen has been shown to yield higher progression-free survival rates than ABVD among previously untreated patients. Trials in which ABVD and escBEACOPP have been directly compared have not shown a significant difference in overall survival, but a meta-analysis of several studies has suggested that the 5-year survival rate may be 5 to 10 percentage points higher with escBEACOPP than with ABVD. These results should have been confirmed by a direct comparison between both protocols in a phase III trial with enough number of patients and follow-up but with the new drugs in HL such a trial will never be made. This increment (escBEACOPP over ABVD) is achieved at the cost of significantly increased short-term and long-term toxic effects. EscBEACOPP (6 to 8 courses) carries the risk of permanent infertility and prolonged fatigue, and myelodysplasia or acute leukemia are more frequent (1.6 to 2%) than with ABVD (<0.5%). Although ABVD is generally associated with acceptable adverse-event rates, it carries the risk of serious pulmonary toxic effects as a result of the bleomycin exposure and cardiac toxicities mostly in the elderly. Since the first studies comparing BEACOPP to ABVD two different options have been proposed based on early PET evaluation.
- The first option is to begin treatment with ABVD than to increase in early positive PET with escBEACOPP and to decrease in the remaining omitting Bleomycin. Results for the 85% of patients with early negative PET are excellent with a 3-year PFS at 85% similar for patients receiving or not Bleomycin after response.

- The second option is to begin treatment with escBEACOPP and to decrease to ABVD × 4 courses in early PET2 negative (87%), this option has randomly been compared to 6 escBEACOPP and show a 5-year PFS at 86% not different from 6 escBEACOPP.10

The two series are not comparable in term of advanced patients with 40% stage II in the first one versus only 10% in the second. Both strategies can be applied but young and advanced patients (e.g., with bulky mediastinum) benefit more of escBEACOPP early in their disease course. Treatment with only 2 esc BEACOPP reduces dramatically the toxicities related to this regimen when given for 6 cycles.

The recent HD18 study from the GHSG has confirmed no need of consolidation radiotherapy in post-chemo PET-negative patients and the possibility to limit the number of escBEACOPP to four without loss of tumor control.11 Another approach is to omit procarbazine and replace by dacarbazine like in the pediatric protocols with this substitution the rate of infertility and second cancer has diminished.12

Targeted therapies

CD30 is a characteristic surface antigen expressed on Reed–Sternberg cells in cHL. Brentuximab vedotin (Adcetris®) is an antibody–drug conjugate composed of an anti-CD30 monoclonal antibody conjugated to the monomethyl auristatin E. Adcetris® has been approved in 2011 for the treatment of cHL after failure of autologous stem-cell transplantation or after two or more multiagent chemotherapy regimens in patients who are not candidates for transplantation. A previous phase 1, dose-escalation trial involving patients with advanced Hodgkin’s lymphoma evaluated the use of frontline Adcetris® combined with doxorubicin, vinblastine, and dacarbazine (A+AVD) had an acceptable side-effect profile in the absence of bleomycin®.

On the basis of these findings, ECHELON-1, a large, international, open-label, randomized, multicenter, phase 3 trial was conducted to compare A+AVD with ABVD as frontline therapy in patients with stage III or IV cHL. This large international study has just been presented on 1334 patients and show a 5% benefit of the experimental arm with Adcetris®. In intent to treat, the 2-yr progression free survival was at 82%.12 This study is difficult to compare to previous studies for many reasons. First, inclusion criteria regarding to age and stage are not the same. Second, the primary endpoint was a modified progression free survival taking in account progression and death but also detection of a response that was less than complete at the end of primary chemotherapy (Deauville score of 3, 4, or 5 on a PET scan), followed by the delivery of subsequent antitumor therapy. This criterion is difficult to compare and now most PET-guided studies consider that a Deauville score of 3 is a complete remission.14,15 Third, Echelon1 was not a PET-guided study and cannot be compared to the more recent studies based on early PET2 evaluation. Adcetris® has also been used with BEACOPP replacing both vincristine and bleomycin (BrECAPP regimen) and procarbazine was replaced by dacarbazine and prednisone by dexamethasone giving the BrECADD regimen both have shown high response rates in a phase II study.16 cHL is characterized by malignant Hodgkin Reed-Sternberg (HRS) cells dispersed within an extensive inflammatory/immune cell infiltrate. HRS cells frequently harbor alterations in chromosome 9p24.1, leading to overexpression of programmed death-ligand 1 (PD-L1) and PD-L2, ligands of the programmed death 1 (PD-1) immune checkpoint receptor. For these reasons relapsed/refractory HL have been treated with nivolumab and pembrolizumab with high response rates from 60 to 80% in phase 1.12,13 They are now used in first relapse and may be incorporated in first line in association with AVD.

Conclusions

First line treatment in cHL has improved in many ways. The omission of radiation therapy in advanced stages then in some early stages will decrease long-term effects. Second, the use of early PET at two cycles allows to decrease treatment in good responders and to increase it in bad responders. Third, targeted therapies are now incorporated in first-line and may change therapeutic decisions. Unfortunately, no biological features have been shown to help for therapeutic decision but this may change in next years with new genomic data and minimal residual disease.

Table 1. Large randomized trials in advanced cHL before the PET guided strategy.

| Chemotherapy                  | NB | Disease control | Survivals |
|-------------------------------|----|-----------------|-----------|
| GHSG HD15                     | 8 escBEACOPP | 705 | 5 yr PFS | 85.6% | 92% |
|                               | 6 escBEACOPP | 711 |           | 90%  | 95% |
| Gruppo Italiani               | 6/8 ABVD | 168 | 4-yr PFS | 73%  | 84% |
|                               | 4 escBEACOPP + 4 standardBEACOPP | 163 | 4 yr PFS | 85%  | 89% |
| Intergroup EORTC/LYSA         | 8 ABVD | 275 | 4 yr PFS | 73%  | 90.3% |
|                               | 4 escBEACOPP + 4 standardBEACOPP | 274 |         | 83.4% | 92% |

ABVD: Doxorubicin, bleomycin, vinblastine, and dacarbazine; escBEACOPP: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; PFS: progression free survival.
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First PET guided study with BEACOPP.

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