

Interim-Response-Adapted Therapy in Advanced Hodgkin's Lymphoma: Current Status

It has been 6 years after our initial publication of a phase II trial of response-adapted therapy (RAT) in advanced Hodgkin's lymphoma (aHL), which was one of the first prospective studies published using RAT in aHL.^[1] We had treated patients with aHL (defined as Stage IIB, III, and IV) with two cycles of ABVD and then performed an interim positron emission tomography/computed tomography (iPET-CT) scan iPET2. Those who had a Deauville score (DS) of 4 or 5 received four cycles of escalated BEACOPP (EB) and those with DS 1–3 continued 4 more ABVD. The disease-free survival (DFS) at 2 years was 76%, and overall survival (OS) was 88%. With more mature follow-up, the DFS at 5 years was 77%, and OS was 85% for the entire cohort of 50 patients.^[2] The survival was inferior among iPET2+ (5-year DFS [50%] and OS [62%]) versus iPET2–ve patients (5-year DFS [82%] and OS [85%]). These results have been replicated in much larger multicenter studies globally, and RAT has been accepted as one of the standard modes of treatment in aHL.

Context of the Study Scenario in 2010–2011

PET-CT scanning was available at the Cancer Institute from 2007. However, this was used only for staging and end therapy assessment and not for treatment tailoring. The Indian data^[3] suggested that only about 70% of patients with aHL were cured with ABVD, and we needed to do better. Strong data favored the use of EB (GHSG HD9 study),^[4] but the toxicities were a concern. We needed some way to identify those who would “fail” ABVD. The International Prognostic Scoring System had significant limitations in identifying “high risk” subsets. Emerging data suggested that iPET2 could identify a “very high risk” subset and also the possibility of adapting therapy based on iPET2.^[5,6] On this background, the iPET2-adapted study was designed.

Study Design and Other Challenges

How to interpret the interim positron emission tomography 2?

The prognostic value of iPET 2 was known, but the challenge was to have a standard definition of what was positive and negative. This was discussed worldwide, and the recommendations of the International Harmonization Project were published.^[7,8] Although the term “DS” was not yet popular, we had a guideline which was easy to use and reproducible and appropriate for a clinical trial situation.

Can we deliver escalated BEACOPP safely?

The original HD9 trial had reported a significant increase in toxic deaths with the use of EB.^[4] Based on our discussions with the authors of GHSG HD9, we incorporated the following safeguards while delivering EB: routine use of G-CSF from day 9 and prophylactic antibiotics. Initially, all patients requiring EB were treated as inpatients till the recovery of counts. Later with more experience, some patients were treated as outpatients. Although half our patients developed febrile neutropenia, there were no toxic deaths in our study.

How to fund the delivery of escalated BEACOPP?

The cost of chemotherapy in EB is almost similar to ABVD as traditional agents with available generics are used. However, the cost of supportive care (antibiotics, inpatient care, and growth factors) is higher because febrile neutropenia occurs in half the patients. This is a concern in private practice when patients are paying out of pocket.

Study design, sample size, and enrolment

Large sample sizes are a challenge in single-center studies. We calculated the sample size for the entire group of patients instead of only for the PET positive cohort. By aiming for a DFS of 85% for the group as a whole, we estimated a sample size of 50 for a power or 80% with 5% alpha. As EB had already demonstrated a DFS of 85%, we felt that anything lower than 85% would be unacceptable.

Response-Adapted Therapy in Advanced Hodgkin's Lymphoma – What Have we Learnt?

Since the publication of our study, several large trials [Table 1] have been published which have looked at iPET2-guided therapy in aHL. There are two approaches in RAT:

- i. Start with ABVD and then tailor therapy based on iPET2 (“Chronos”) or
- ii. Start with EB and then tailor therapy based on iPET2 (“Kairos”).

The following can be inferred from the available studies:

- DS is simple and it works
 - DS had good reproducibility, acceptable interobserver variability and is easy to interpret making it a practical tool for routine patient care
- Positive iPET (DS 4,5) after 2 cycles is seen in 10%–20% of patients after 2 cycles
 - Therapy escalation improves the outcomes of iPET2+ve patients

Table 1: Studies of response-adapted therapy in advanced Hodgkin's lymphoma

Study	Phase	Initial Rx	Approach after iPET2	5 years-DFS/EFS/PFS		Remarks
				iPET2 negative, %	iPET2 positive, %	
Press <i>et al.</i> ^[9,10] SWOG S0816	2	ABVDX2	Positive: EBX4 Negative: ABVDX4	76	66	25% of PET negative patients relapsed
Johnson <i>et al.</i> ^[11,12] RATHL-CRUK/07/033	3	ABVDX2	Positive: EBX4 or SB14 X4 Negative: AVD versus ABVD	83	66	Deescalation to AVD in PET2 negative was noninferior
Gallamini <i>et al.</i> ^[13] GITIL/FIL HD0607	3	ABVDX2	Positive: EB versus R-EB Negative: ABVDX4	87 (3 years)	60 (3 years)	Radiotherapy did not impact those who had bulky but were PET negative
Borchmann <i>et al.</i> ^[14] HD18-GHSG	3	EBX2	Positive: 6XEB or R-EB Negative: 4XEB versus 6XEB	91	88	48% were PET2 positive did not use DS. iPET2+: No impact on outcome
Zinzani <i>et al.</i> ^[15] HD0801	2	ABVDX2	Positive: Salvage IGEV f/b HDT Negative: ABVD	81 (2 years)	76 (2 years)	20/103 patients did not undergo ASCT and received only ABVD
Casasnovas <i>et al.</i> ^[16] AHL2011-LYSA	3	EBX2	Positive: Continue EB Negative: ABVD versus EB	88	68	84% were eligible for deescalation

DFS – Disease-free survival; EFS – Event-free survival; PFS – Progression-free survival; PET – Positron emission tomography; iPET – Interim PET; EB – Escalated BEACOPP; ASCT – Autologous stem-cell transplantation; DS – Deauville Score; AVD – Doxorubicin, vinblastine and dacarbazine; ABVD – Doxorubicin, bleomycin, vinblastine, dacarbazine; HDT – High-dose therapy; IGEV – Ifosfamide, vinorelbine, gemcitabine, etoposide

- Escalated therapy in iPET2 + patients yielded better results (50%–68% 5-year event-free survival [EFS]) than those reported historically with continued ABVD (<20% 5-year EFS)
- “Kairos approach” seems to be having better EFS (90%–95%) than “chronos” approach (80%–85%) (Caveat: this conclusion is based on cross-trial comparisons)
- Starting with EB in AHLL trial seemed to reduce the PET2 + vity rates (12%)
- Overall outcomes seem to be better than those seen with escalation trials^[16]
- Deescalation to AVD in iPET2 negative reduces the risk of bleomycin toxicity
- Deescalation to AVD was noninferior to the continuation of ABVD in iPET-2 negative patients in the RATHL study – this was a significant finding which when applied to clinical practice reduces the risk of fatal bleomycin lung toxicity.

Limitations of Response-Adapted Therapy

The original retrospective data with iPET2 showed a very strong negative predictive value for a negative scan with these patients enjoying the survival of 90%–95%.^[5,17] Unfortunately, in all prospective studies starting with ABVD, the survival in the PET2–ve has been more modest (76%–87%). Although RAT (therapy escalation) does improve the survival in PET-2+ve patients (compared to continued ABVD), there are two key limitations:

- A subgroup of patients (15%–20%) who fail therapy despite having negative iPET2. We need better markers to identify the poor risk subsets even among those who are iPET2-ve

- Outcome of iPET2+ve patients, even after escalation, is only 50%–60% (EFS) and needs to improve further. We need better interventions than EB in these patients.

Tools for better identification of the poor risk groups

The International Prognostic Score has limited ability in identifying the subsets of patients who have the survival of <50%–60% in the modern era. There are some data to suggest that CD68 expression and patterns of PD-1 expression can predict for inferior survival even among PET–ve patients.^[18] These biomarkers needs to be refined further to identify the “poor” subsets among iPET2–ve. Interestingly, in studies which used EB upfront (the “Kairos” approach), EFS was 88%–91%, which (keeping all the caveats of cross-trial comparisons) does seem better than that achieved with ABVD followed by escalation (the “chronos” approach).^[14,16]

Better therapy for the interim positron emission tomography 2 positive patients

The study which used autotransplant as consolidation (instead of BEACOPP) reported a survival of 76% in iPET2+ve patients, which is the highest reported so far.^[15] The HD18 trial showed excellent survival even among PET2+ve patients, but the methodology used to define positivity was not standard (DS was not used). Nearly half patients in HD18 had positive iPET2 (compared to 12% in the AHL2011 study which also started with 2 EB). Incorporation of nivolumab or brentuximab may improve the survival in this subset, but at present, data are lacking.

Traditional	Response adapted therapy (RAT)		Added targeted therapy
ABVDx6	Start with ABVD and then adapt based on iPET2 ("Chronos") ABVDX2 then interim PET +ve: EB or SB X4-6 -ve: AVD X4 or ABVD X4	Start with EB and then adapt based on iPET2 ("Kairos") EBX2 then interim PET +ve: continue EB -ve: ABVDX4	AVD+Brentuximab
Advantages			
Universally applicable EFS~70-75% ~50% of relapses salvageable	Only 10-20% need EB Reduction to AVD- ↓Bleomycin toxicity	Best EFS reported >90% 80-85% can be de-escalated	Survival is superior to ABVD in phase III trial
Disadvantages			
EFS inferior to ABVD alone (cross trial comparison) Bleomycin toxicity is a concern	Requires access to PET EFS inferior to Kairos (cross trial comparison)	Requires access to PET All patients exposed to acute toxicity of EB at least for 2 cycles	Cost of therapy is very high EFS inferior to EB-based approaches (cross trial comparison)
Evidence			
GHSg-HD 9	RATHL GITIL/FIL HD0607	GHSg-HD-18 AHL2011-LYSA	ECHELON-1

Figure 1: Summary of current approaches to treatment of Hodgkin's lymphoma

Response-Adapted Therapy with the "Chronos" Approach May Be an Optimal Approach for Indian Patients Who Have Access to Positron Emission Tomography-Computed Tomography

Current standard treatment approaches for aHL are summarized in Figure 1. Among these, RAT is a useful "middle path," which is suitable for use in our context, provided one has access to PET-CT scans.

Compared to earlier data from the Indian centers (5-year EFS of 70%–75% with ABVD X6), RAT produces the survival of about 80%–85% which is an improvement.^[1-3,19] An important caveat here is the effect of "stage migration" when we are comparing patients staged by CT scans versus patients staged by PET-CT.

An additional advantage of the PET-guided therapy is the option for deescalation to AVD based on the RATHL results in iPET2–ve patients. In fact, the removal of bleomycin in cycles 3–6 has nearly eliminated deaths due to bleomycin pulmonary toxicity in aHL patients.

BEACOPP toxicity is a challenge in the Indian context where we have to deal with patients from the poor economic and social backgrounds. Patients have to understand the importance of reporting on time when they develop febrile neutropenia. Moreover, hospitals have significant space constraints and may not be able to admit these patients when required. If these aspects can be taken care, EB can be delivered in India as demonstrated by our

study. Because of these reasons, the "Kairos" approach may not be feasible in India where all patients would receive at least two cycles of EB.

If one wants to try the "chronos" model but is unable to deliver EB, one option is to use 4–6 cycles of BEACOPP-14 in iPET2+ve patients. This is much less toxic and can be easily delivered without requirement for admissions. BEACOPP-14 was found as effective as EB (non-randomized comparison) in the RATHL study.^[11] Recent reports from a multicenter analysis have shown that RAT can be safely practiced in the Indian conditions.^[20]

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Submitted: 28-Dec-2019

Revised: 02-Jan-2020

Accepted: 06-Jan-2020

Published: 17-Feb-2020

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Access this article online	
Quick Response Code: 	Website: www.ijmpo.org
	DOI: 10.4103/ijmpo.ijmpo_276_19

How to cite this article: Ganesan P. Interim-response-adapted therapy in advanced Hodgkin's lymphoma: Current status. *Indian J Med Paediatr Oncol* 2019;40:566-9.