

Hodgkin: Update 2018 - Section 3

Relapsed/refractory Hodgkin lymphoma

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Take Home Messages

- For younger patients without co-morbidities, the standard of treatment for RR-HL remains salvage chemotherapy and autologous stem cell transplantation (ASCT).
- Novel targeted agents such as brentuximab vedotin, nivolumab and pembrolizumab, established in single-arm trials in the post-ASCT RR-HL setting, are now also being studied as salvage strategies pre-ASCT.
- Biomarkers, both prognostic and predictive, are urgently needed in this challenging patient group, to allow risk-adapted treatment approaches.

Abstract

Effective treatment strategies exist for patients with relapsed and refractory Hodgkin Lymphoma (RR-HL): autologous stem cell transplantation (ASCT) continues to be the standard of care but most salvage and conditioning regimens have not been evaluated in randomized trials. For those patients not eligible for ASCT, or those with multiply relapsed HL, the advent of novel therapeutics with promising single-agent activity may represent a paradigm shift with regards to disease control and outcome. In selected cases, allo-SCT may continue to play a role in achieving long-term disease-free survival.

Introduction

The majority of patients with HL can expect to be cured from their disease by frontline therapy, but up to 20% of patients who achieve a treatment response will subsequently relapse after completion of treatment.¹ Refractory disease is usually defined as non-response or progression within 90 days of treatment completion, whereas relapsed disease is considered to be early (within 3-12 months of first treatment) or late (>12 months following first treatment).^{2,3} Confirmation of disease histology in suspected RR-HL is generally advisable if salvage treatment is considered, especially because the positive predictive value of post-treatment FDG avidity on PET scan can be variable, and other causes should be excluded.⁴

Prognostic factors

Older, retrospective studies have consistently identified time to relapse after first treatment (<12 months), presence of advanced stage or extranodal disease at relapse, and poor performance status as predictors of poor outcome,^{5,6} whereas more recently, lack of chemosensitivity to pre-ASCT salvage therapy and residual disease at the time of ASCT have been recognized as impor-

tant risk factors.^{7,8}

Functional imaging after salvage chemotherapy has become increasingly useful as a predictive biomarker for response assessment: a negative PET scan after salvage treatment may be predictive of improved progression-free survival (PFS) post-ASCT, whereas residual PET positivity was shown to be associated with poorer post-ASCT outcomes, even if a partial response (PR) had been achieved by conventional CT imaging.⁹ A recent meta-analysis of 745 RR-HL patients undergoing ASCT found a reduced PFS and OS in PET positive patients compared to those achieving PET negativity following salvage chemotherapy.¹⁰ Understanding the biology underlying RR-HL may offer a better approach to predicting prognosis, and the recently developed RHL30 prognostic assay, based on gene expression profiling of HL relapse samples, was able to predict unfavorable post-ASCT outcomes in two independent external validation cohorts.¹¹

Salvage and ASCT

A number of primary salvage regimens are described in the literature (Table 1). Efficacy has usually been reported in single arm Phase II studies but no randomized comparisons have been carried out.¹² In the absence of a gold standard salvage regimen, important factors to take into consideration are acceptable toxicity, effect on stem cell mobilization and context of delivery, such as an outpatient setting.

Increasingly, newer combinations incorporating agents such as bendamustine (e.g. in combination with gemcitabine and vinorelbine (BeGV regimen)), brentuximab vedotin (BV) and checkpoint inhibitors are being evaluated.¹³ Alternatively, salvage with single-agent BV allowed 28-35% of patients to proceed with ASCT without further chemotherapy, whereas an additional 35-40% of patients achieved PET negativity after sequential chemotherapy and were able to undergo ASCT.¹⁴ Secondary salvage in patients who fail to achieve at least a PR to first line salvage regimens is possible and a number of patients

may achieve good outcomes with second-line, non cross-resistant salvage therapies. The available data in this area, however, is predominantly based on small retrospective cohort studies.^{15,16}

High dose chemotherapy and ASCT

The rationale for high dose therapy and ASCT was established by two randomized trials which demonstrated a significant advantage in PFS in this patient group although there was no difference in OS.^{17,18} Both these studies used BEAM (carmustine, etoposide, cytarabine, melphalan) as the conditioning regimen, but other regimens have been evaluated largely in institutional series reporting comparable toxicities and outcomes.¹⁹ High dose sequential strategies (HDSS) or tandem ASCT have not clearly demonstrated improved outcomes in patients with RR-HL.^{20,21}

Post-ASCT consolidation approaches

Post-ASCT consolidation with radiation, mainly to sites of bulk, residual disease, or localized relapse may be of benefit, although there are no randomized comparisons.^{22,23} Post-ASCT maintenance has been evaluated in the AETHERA study which randomized 329 high risk RR-HL patients to either BV or placebo as consolidation therapy for up to 16 cycles of planned treatment and reported PFS of 42.9 months in the BV group *versus* 24.1 months in the placebo arm although this did not result in an OS advantage.⁸

Allo-SCT

The role and timing of allo-SCT in the setting of RR-HL remains poorly defined. Early approaches using myeloablative conditioning regimens reported unacceptable rates of TRM. Reduced-intensity conditioning approaches showed the feasibility of various stem cell sources, including sibling (SIB), matched-unrelated donor (MUD) and umbilical cord blood, with PFS and OS of 20-40% and 40-60%, respectively.²⁴⁻²⁷ In addition, a recent retrospective EBMT study found that post-transplantation cyclophosphamide-based haploidentical (HAPLO) transplantation leads to similar survival outcomes compared with SIB and MUD, and suggested that HAPLO may result in a lower risk of chronic graft-versus-host-disease (GvHD) than MUD transplantation.²⁸

Targeted therapies

The CD30 antibody-drug conjugate BV was evaluated in a pivotal Phase II trial in RR-HL patients after ASCT failure. The ORR was 75%, and 34% of patients achieved CR. At 5-year follow-up, responses were shown to be durable, with those patients in CR having an OS of 64%, and 9% achieving a CR without any further treatment.^{29,30} Nivolumab and pembrolizumab are monoclonal antibodies to PD-1 which have significant activity in RR-HL although follow-up remains early. The phase II study of nivolumab showed ORR of 66.3% and a CR rate of 9% in patients in relapse post-ASCT

Table 1. Salvage regimens in RR-HL.

Salvage regimen	No. of patients	ORR (%)	PR (%)	CR (%)	Reviewed in/References
Established/traditional regimens					
Ifosfamide-based					
ICE (ifosfamide, carboplatin, etoposide)	65	88	59	26	12,38
IVE (ifosfamide, epirubicin, etoposide)	46	85	24	37	12,38
IV (ifosfamide, vinorelbine)	47	83	38	45	12,38
IVOx (ifosfamide, etoposide, oxaliplatin)	34	76	--	32	12,38
MINE (mitoxantrone, ifosfamide, vinorelbine, etoposide)	100	75	39	34	12,38
IGEV (ifosfamide, gemcitabine, vinorelbine)	91	81	28	54	
Platinum-based					
GDP (gemcitabine, dexamethasone, cisplatin)	23	69	52	17	12,38
GEM-P (gemcitabine, cisplatin, methylprednisolone)	21	80	52	24	12,38
DHAP (dexamethasone, cytarabine, cisplatin)	102	89	68	21	12,38
DHA0x (dexamethasone, cytarabine, oxaliplatin)	23	73	30	43	12,38
ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin)	22	73	32	41	12,38
ASHAP (doxorubicin, methylprednisolone, cytarabine, cisplatin)	56	70	36	34	12,38
Other					
Dexa-BEAM (dexamethasone, carmustine, etoposide, cytarabine, melphalan)	144	81	54	27	12,38
Mini-BEAM (carmustine, etoposide, cytarabine, melphalan)	55	84	32	50	12,38
GVD (gemcitabine, vinorelbine, liposomal doxorubicin)	91	70	--	19	12,38
More recent (Bendamustine or BV-based)					
Bendamustine	36	53	19	33	12,38
BeGEV (bendamustine, gemcitabine, vinorelbine)	59	83	10	73	13
BV (brentuximab vedotin)	46	--	--	27	14
BV-augICE (brentuximab vedotin, augmented ICE)	33	--	--	66	14
BV-Bendamustine	64	78	--	--	34
BV-DHAP	12	100	--	100	35
BV-ESHAP	27	100	--	89	36
BV-nivolumab	42	90	--	62	37

and BV.³¹ Pembrolizumab was shown to have similar efficacy in a Phase II study in patients who had failed ASCT and BV (ORR 71%, CR 22%).³² One clinical concern with using PD1 blockade is that patients who have been treated with checkpoint inhibitors may be more prone to GvHD following allo-SCT.³³ These agents are now being evaluated in the salvage therapy setting raising important questions regarding post-ASCT outcomes, re-treatment, and outcomes post treatment failure.

Conclusions

Conventional salvage and ASCT remain the standard treatment for younger patients with RR-HL. The emergence of novel agents such as BV and immune checkpoint inhibitors has opened up great opportunities to improve the survival of patients in the relapse setting. Novel therapies also appear particularly useful for patients who have chemo-resistant disease or are not candidates for SCT. Despite these advances, many challenges and questions remain in RR-HL including the role of radiation therapy, integrating novel agents earlier in the treatment course and the pursuit of new biologic insights to improve patient outcome.

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