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Advances in Therapy for Relapsed or Refractory Hodgkin Lymphoma

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Abstract

Purpose of review The landscape of relapsed or refractory (R/R) Hodgkin lymphoma (HL) treatment has changed significantly since the FDA approval of brentuximab vedotin in 2011. In this review, we summarize the recent advances in the therapy for R/R classical Hodgkin lymphoma (cHL).

Recent findings Immunotherapies with pembrolizumab, nivolumab, and ipilimumab, and chimeric antigen receptor (CAR) T cell therapies have shown promising results in early phase trials. Other novel agents under investigation include targeted therapies with histone deacetylase inhibitors, Janus kinase 2 inhibitors, and immunomodulators.

Summary While further studies with larger populations and longer follow-up times are needed to determine the safe and effective combinations, these novel approaches represent a growing list of treatment options that are on the horizon to improve the cure rate and increase duration of remission for R/R HL patients.

Keywords Relapsed/refractory · Hodgkin lymphoma · Brentuximab vedotin · Nivolumab · Pembrolizumab

Introduction

Patients with classical Hodgkin lymphoma (cHL) have favorable outcomes with a 5-year overall survival of 87% [1]. However, 10 to 15% of patients with limited-stage disease and 30 to 40% with advanced stage will relapse after a front-line therapy [2, 3] and require further treatment. The standard of care for relapsed or refractory cHL (R/R cHL) is salvage chemotherapy followed by autologous stem cell transplantation (ASCT). The landscape of R/R cHL treatment has changed significantly since the FDA approval of brentuximab vedotin (BV) in 2011 for the treatment of R/R cHL patients who are transplant-ineligible after two or more chemotherapy regimens and for treatment of patients with ASCT failure. More recently, the FDA approval of the checkpoint inhibitors pembrolizumab and nivolumab for the treatment of patients whose cHL has relapsed after three or more lines of therapy and patients who relapsed after ASCT or post-transplantation BV, respectively, has increased further the treatment options for R/R HL patients. Other novel agents under investigation include histone deacetylase (HDAC) inhibitors, Janus kinase 2 (JAK2) inhibitors, and immunomodulators as well as early approaches with chimeric antigen receptor (CAR) T cells. In this review, we summarize the recent advances in therapy for R/R cHL.

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"Traditional" Salvage Chemotherapy

Progression-free survival (PFS) and freedom from treatment failure (FFTF) benefits of high-dose chemotherapy plus ASCT over chemotherapy alone in R/R HL were shown in randomized trials [4, 5], but the optimal salvage regimen of multiagent chemotherapy prior to ASCT consolidation has not been conclusively established. There are no randomized clinical trials demonstrating superiority for any one of the standard second-line chemotherapy regimens; choice of regimen should be based on patient comorbidities, convenience, prior treatment history, and physician and patient preference.

Commonly used regimens include platinum-based therapies such as DHAP (dexamethasone, high-dose cytarabine, cisplatin), ESHAP (etoposide, methylprednisolone, high-dose cytarabine, cisplatin), and ICE (ifosfamide, carboplatin, etoposide) with reported overall response rates (ORRs) ranging 73 to 100% [6–9], and gemcitabine-based regimens GVD (gemcitabine, vinorelbine, liposomal doxorubicin), IGEV (ifosfamide, gemcitabine, vinorelbine), and GDP (gemcitabine, dexamethasone, cisplatin) reporting ORRs of 70 to 81% [10–12]. Despite these impressive ORRs, the complete response (CR) rates with these regimens are 21–67% for platinum-based regimens and 17–54% for gemcitabine-based regimens; this lower CR rate makes the utility of these therapies as a bridge to ASCT limited to those patients who have optimal or near optimal disease control. The common toxicity with these regimens is significant myelosuppression, which can be managed with supportive care in most patients, but extensive treatment may impair stem cell mobilization. Various approaches have been studied to improve the outcomes of transplantation, including sequential high-dose chemotherapy prior to ASCT [13], response-adapted strategy based on the PET/CT findings after the second cycle of salvage chemotherapy [14], maintenance therapy after transplantation, and more recently, incorporation of BV in the pre-ASCT salvage regimens.

BV-Incorporated Salvage Regimens

Brentuximab vedotin is an antibody-drug conjugate (ADC) composed of an anti-CD30 monoclonal antibody linked to an anti-microtubule agent [15–17]. Once internalized in CD30-expressing cells, the linker is cleaved by a protease and the active agent monomethyl auristatin E (MMAE) is released, causing cell cycle arrest and apoptosis. CD30 is a surface antigen characteristically expressed on the malignant Hodgkin Reed-Sternberg (HRS) cells of cHL but has a restricted expression profile on normal tissues, making it an ideal therapeutic target in cHL [18, 19].

Brentuximab vedotin has been evaluated in combination with traditional salvage regimens with comparable response rates. The BRaVE study reported a metabolic CR rate of 79% when BV was incorporated into DHAP [20]. Similarly, the PET-based CR rate for addition of BV on days 1 and 8 of the ICE regimen was 70% by central independent review and 87% by investigator review [21], and for BV plus ESHAP was 70% [22]. The toxicity of combining BV with traditional salvage chemotherapy regimens is, most notably, increased neuropathy and myelosuppression; however, they are generally manageable because increased neutropenia does not translate to increased risk of febrile neutropenia, and peripheral neuropathy is resolved with dose reduction or, in few cases, discontinuation [22]. A combination of BV and bendamustine has shown promising results at the standard doses of BV administered on day 1 and bendamustine on days 1 and 2 of a 21-day cycle. In a phase I/II study, this regimen showed an ORR of impressive 93% with 74% achieving CR, allowing 76% of patient to undergo ASCT, and a 2-year overall survival (OS) of 95% for those who underwent transplantation [23]. Fifty-six percent of patients experienced infusion-related reactions (IRRs), which led to a protocol change requiring high-dose corticosteroid and antihistamine premedication. This amendment decreased the IRRs leading to treatment discontinuation from 24 to 7% but did not improve the incidence of IRRs significantly. The 2-year progression-free survival (PFS) was 70%. A subsequent single-center study of 20 patients that evaluated the higher dose of bendamustine at 120 mg/m^2 administered on days 2 and 3 following BV on day 1 (bendamustine supercharge (Bs)), based on the hypothesis that high-dose bendamustine given after BV may have synergistic effect, reported 80% of patients achieving a Deauville score of 2 or less, deemed the most important predictor of favorable post-ASCT outcome, hematopoietic stem cell transplantation (HSCT) rate of 90%, and a 2-year PFS of 94% at the expense of a higher toxicity than either agent as monotherapy [24].

Post-ASCT Consolidation Therapy

Until the AETHERA study which led to the 2015 FDA approval of BV for post-ASCT BV-naïve patients as a consolidation treatment, there was no standard for maintenance therapy following ASCT in HL. The challenge in this context is for an agent that is both active and well-tolerated for extended dosing, in post-ASCT patients who may be more vulnerable to myelosuppression. In the AETHERA study, post-ASCT cHL patients at high risk of relapse or progression, defined as primary refractory cHL; relapsed HL within 12 months of initial remission; or relapsed disease with extra-nodal involvement at the initiation of pre-transplantation salvage chemotherapy were randomized to receive BV or placebo starting 30–45 days after transplantation [25]. Median PFS favored BV maintenance (42.9 months) compared with placebo (24.1 months), but there was no significant difference in OS, which could have been confounded by the allowance of cross-over of patient in the placebo group to BV. The PFS benefit was consistent across the prespecified subgroups of all three high-risk features for relapse or progression, namely, primary refractory patients, patients with early relapse after frontline therapy, and patients with extra-nodal disease at initiation of salvage therapy, but was also seen in younger patients (< 45 years of age), females, patients with ECOG status of 1, heavily pre-treated patients (with more than 2 systemic pre-ASCT treatments), and patients with B-symptoms after frontline therapy. A post hoc analysis was suggestive of negative

association between PFS benefit and the number of risk factor for relapse/progression. The most frequently reported adverse events (AEs) in the BV arm were peripheral neuropathy in 56% of patients and neutropenia in 35%. These toxicities were significantly more common compared with the placebo group with 16% and 12%, respectively. With the FDA approval, BV became an option for post-ASCT consolidation therapy for BV-naïve high-risk HL patients at 1.8 mg/kg every 3 weeks, initiated within 4–6 weeks following ASCT and up to a maximum of 16 cycles.

The role of checkpoint inhibitor therapy as a post-ASCT maintenance strategy is under investigation. In a phase II trial of pembrolizumab, post-ASCT patients with chemo-sensitive disease received pembrolizumab every 3 weeks for up to 8 cycles, starting within 21 days of ASCT [26•]. The PFS and OS at 18 months were 82% and 100%, respectively. However, 30% of patients experienced grade 3 or worse AEs including transaminitis, pneumonitis, and colitis, leading to treatment discontinuation in 13% of the patients. Current data, though promising, is insufficient to recommend checkpoint inhibitors for a consolidation therapy after an ASCT. Results of ongoing studies of nivolumab as a single agent and a combination of BV and nivolumab as post-ASCT consolidation strategies (Table 1) are eagerly awaited to elucidate the role of programmed death 1 (PD-1) blockade in post-ASCT setting.

Brentuximab Vedotin

Since the approval of BV in 2011 by the FDA for the treatment of patients with relapsed or refractory disease after ASCT or at least two prior lines of multi-agent chemotherapy regimens based on the Pivotal study [27], BV has played an increasingly important role in the treatment of cHL. In a phase II study evaluating the single agent BV as a bridge to ASCT in R/R cHL, the ORR was 75% including 43% CR to second-line BV, and 50% of the patient were able to proceed to ASCT without further chemotherapy [28].

In addition to its incorporation in the traditional salvage chemotherapy regimens prior to ASCT, its role in the consolidation therapy in the post-ASCT setting, and as a second-line treatment option as a single agent, BV is used in combination with chemotherapy for the treatment of patients with previously untreated stage III or IV disease [29••]. However, as BV becomes integrated into earlier lines of therapy, the impact of this on its role as a salvage therapy is yet to be determined. For patients who are refractory to BV-containing upfront chemotherapy, it likely will have little utility as a salvage therapy. For patients with relapsed disease, however, the data suggests that retreatment with BV may be effective in some patients. In a phase II study of patients with CD30-positive HL or systemic anaplastic large cell lymphoma (ALCL) who relapsed after achieving CR or partial response (PR) with BV, 12 of 20 (60%) HL patients achieved an ORR including 30% CR, suggesting that a retreatment with BV can be active [30]. The median duration of response for all HL patients was 9.2 months, and 9.4 months for patients who achieved CR. Other innovative approaches using BV in the relapsed or refractory setting have involved its combination with other agents including immunotherapy.

Immunotherapy

HRS cells are the primary malignant cells in HL but account for only a minority of cells in affected lymph nodes, as few as 0.1%; they are surrounded by a background of mixed inflammatory cells. In addition to CD30 expression on the HRS cells, another hallmark of HL pathogenesis is the maintenance of appropriate immune microenvironment that sustains the proliferation and survival of HRS cells. Chromosomal analyses of HRS cells have shown that they frequently harbor a 9p24.1 amplification, leading to upregulation of PD-1 ligands and JAK2 [31–33], making PD-1 inhibitors an ideal targeted therapy for HL.

The first anti-PD-1 antibody to be approved by the FDA for R/R cHL treatment was nivolumab. In the phase II CheckMate-205 study of patients who failed ASCT, ORR of nivolumab was 69% including CR rate of 16%, median duration of response of 16.6 months, and median PFS of 14.7 months [34]. In contrast to traditional chemotherapies, durable responses were seen even in patients with PR, and the patients with stable disease (SD) had a similar 1-year OS of 98% as patients with CR (100%), suggesting clinical benefit beyond patients with objective responses. Sixty-one percent of patients with perceived clinical benefit who were treated beyond conventional disease progression, according to the 2007 International Working Group criteria for malignant lymphoma, had stable or reduced tumor burdens. Safety profile was acceptable, with serious nivolumab-related AEs occurring in 12% of patients, and no deaths related to the drug. The high ORR, durable efficacy, and acceptable safety profiles were seen regardless of prior BV exposure. The KEYNOTE-087 trial which evaluated a different PD-1 inhibitor pembrolizumab showed remarkably similar findings of efficacy and safety, with a 69% ORR and a 22.4% CR rate and only 4.3% of patients discontinuing treatment due to treatment-related AEs [35].

Combination immunotherapies have shown promising results. The phase I E4412 trial tested the hypothesis that a combination of tumor cell-targeting drug BV, and a checkpoint inhibitor to activate the immune cells of the tumor microenvironment (TME), would be active in R/R HL. The ORR for arms A-C combining BV and ipilimumab, a monoclonal antibody against cytotoxic T lymphocyte antigen 4 (CTLA-4), had an ORR of 67% with a CR rate of 55% in a heavily

Table 1 Selected ongoing clinical trials of treatment in relapsed or refractory classical Hodgkin lymphoma

Trial ID	Study regimen	Phase	Study objective(s)
NCT01896999	BV plus ipilimumab BV plus nivolumab BV plus ipilimumab and nivolumab	I/II	- To determine maximum tolerated dose and dose limiting toxicities - To evaluate CR rate
NCT02408861	Nivolumab plus ipilimumab	I	- To determine safety and efficacy of ipilimumab and nivolumab in relapsed refractory HIV-associated cHL
NCT02927769	BV plus nivolumab	II	- To determine safety and efficacy in children, adolescents, and young adults
NCT03138499	BV plus nivolumab vs. BV alone	III	- To determine safety and efficacy compared with BV alone in patients who have relapsed, are refractory or are ineligible for SCT
NCT03618550	Pembrolizumab plus GVD	II	- To establish safety of pre-ASCT pembrolizumab plus GVD - To evaluate CR rate to pembrolizumab plus GVD
NCT03179917	Pembrolizumab plus ISRT	II	- To determine CR rate for early stage R/R cHL patients
NCT02362997	Pembrolizumab	II	- To estimate 18-month PFS rate after ASCT in patients treated with pembrolizumab as early consolidation post-ASCT
NCT03077828	Pembrolizumab plus ICE	II	- To determine CR rate prior to ASCT with combination of pembrolizumab and ICE salvage chemotherapy
NCT03057795	BV plus nivolumab after SCT	II	- To determine 18-month PFS
NCT02824029	Ibrutinib	II	- To determine ORR of single agent ibrutinib in patients with R/R HL ineligible for, or post-ASCT
NCT03739619	Gemcitabine, bendamustine, and nivolumab	I/II	- To evaluate toxicity and determine MTD - To determine efficacy
NCT03681561	Ruxolitinib plus nivolumab	I	- To assess MTD
NCT03947255	BV	II	- To determine safety and efficacy in subjects who experienced CR or PR with BV-containing regimen and subsequently experienced disease progression or relapse
NCT03730363	Pentamidine plus ICE	I	- To evaluate dose limiting toxicity and to determine recommended phase 2 dose of pentamidine in combination with ICE
NCT03697408	Itacitinib and everolimus	I/II	- To evaluate DLTs and to establish recommended phase II dose - To evaluate efficacy as demonstrated by CR rate
NCT03602157	ATLCAR.CD30.CCR4⁎ with or without ATLCAR.CD30⁑	I	- To establish safe dose of ATLCAR.CD30.CCR4 with and without ATLCAR.CD30 to infuse after lymphodepletion with bendamustine and fludarabine
NCT03150329	Vorinostat plus pembrolizumab	II	- To assess safety and tolerability by evaluation of toxicities - To determine MTD and recommended phase II dose
NCT03015896	Nivolumab plus lenalidomide	I/II	- To determine safety and tolerability
NCT02940301	Ibrutinib and nivolumab	II	- To estimate CR rate
NCT04052997	Camidanlumab tesirine§	I	- To determine efficacy and safety
NCT03776864	Umbralisib and pembrolizumab	II	- To estimate CR rate
NCT03013933	BV cyclosporine when given together with verapamil hydrochloride	I	- To evaluate safety and tolerability of combination of BV plus CsA/verapamil
NCT02744612	BV plus ibrutinib	II	- To evaluate CR rate
NCT02227199	BV plus ifosfamide, carboplatin, and etoposide	I/II	- To determine maximum tolerated dose - To gain preliminary assessment of efficacy
NCT02098512	BV following allogeneic stem cell transplant	I/II	- To determine safety and tolerability in children and young adults
NCT01703949	BV with or without nivolumab	II	- To evaluate response rate
NCT03436862	Nivolumab	II	- To evaluate safety and tolerability of nivolumab as maintenance therapy early after ASCT

⁎ATLCAR.CD30.CCR4: Autologous T Lymphocyte Chimeric Antigen Receptor cells targeted against the CD30 antigen with CCR4

⁑ATLCAR.CD30: Autologous T Lymphocyte Chimeric Antigen Receptor cells targeted against the CD30 antigen

§Camidanlumab tesirine: ADC composed of anti-CD25 antibody conjugated to pyrrolobenzodiazepine dimer toxin

pretreated R/R HL [36]. The combination of BV and nivolumab in arms D-E had an ORR of 95% including 65% CR [37]. The triplet regimen of BV plus ipilimumab and nivolumab were evaluated in arms G-I of the same trial and

showed an ORR of 95% with a CR rate of 79%, albeit at the expense of increased grade 3 or worse AEs compared with the BV plus nivolumab doublet [38••]. The therapy was generally well-tolerated in all arms, but there were two incidences of grade 5 pneumonitis in nivolumab-containing arms. Neither median PFS nor OS was reached at a median follow-up time of 0.52 years and 0.82 years, respectively. A follow-up randomized phase II trial comparing the BV plus nivolumab doublet and the triplet is ongoing (Table 1). The combination of BV and nivolumab was evaluated in a phase I/II trial as an initial salvage therapy in R/R cHL, given on a slightly different administration schedule for cycle 1 in which BV was given on day 1 and nivolumab on day 8 [39••]. This showed similar high activity, with an ORR of 82% and a CR rate of 61%, in comparison with ORR of 75% and CR of 43% for single-agent BV [28], as mentioned previously. Similar to the E4412 trial, the combination was well-tolerated with only 8% of patients experiencing immune-related adverse events (irAEs) requiring systemic steroids. Other immunotherapy regimens being evaluated in ongoing trials include a ipilimumab-nivolumab combination in HIV-associated R/R cHL; pembrolizumab in combination with salvage chemotherapy regimens ICE and GVD; BV plus nivolumab in ASCT failure; nivolumab in combination with gemcitabine and bendamustine; and pembrolizumab or nivolumab in combination with a JAK2 inhibitor, a histone deacetylase inhibitor, an immunomodulator, a BTK inhibitor, or a PI3K inhibitor (Table 1).

Radiation Therapy

The role of radiation therapy in the treatment of R/R cHL is unclear. In a retrospective analysis of patients who underwent ASCT, peri-transplantation involved-field radiotherapy (IFRT) was shown to have a marginal and statistically insignificant OS benefit compared with chemotherapy alone [40]. There was no significant difference in the overall population, and the difference in the 3-year OS and PFS rates in patients with limited stage disease at relapse were not statistically significant. Guidelines on the use of radiation therapy in treatment of R/R cHL have recently been updated by the International Lymphoma Radiation Oncology Group [41]. Radiation alone can be considered in highly selected patients who are not candidates of combined modality therapy and have not had previous radiation with initial stage IA-IIA disease.

Allogeneic Transplantation

Up to half of the cHL patients who undergo ASCT experience disease recurrence, and the median OS of such patients is a dismal 2.4 years [42]. Allogeneic stem cell transplantation (SCT) is the only treatment option that offers a good chance of long-term remission, but its use is limited by the significant treatment-related morbidity (TRM). Its place in the treatment of ASCT failure is less clear with the availability of BV and checkpoint inhibitors, but it does remain an option for a select few patients who are young, fit, and with few comorbidities and an available donor.

Novel Approaches

Given their success with targeting CD19, CAR T cell therapies are being evaluated in CD30-positive malignancies including cHL. In a trial of CAR T cells expressing the antigen binding domain of a CD30 monoclonal antibody, 10 R/R HL patients including 7 with prior BV exposure received the CD30 CAR-T infusion after FluCy lymphodepletion [43]. Six of the 9 evaluable patients (67%) had a CR, and 4 of the patients experienced grade 1 cytokine release syndrome (CRS) and 6 patients maculopapular rash. In a larger phase I/II trial with 24 heavily treated patients with a median of 7.5 lines of therapy, including 22 HL patients, 10 of 19 (53%) patients in the efficacy analysis population achieved a CR at 6 weeks after the CAR T cell infusion following a bendamustine/fludarabine lymphodepletion [44]. The median PFS was 164 days at a median follow-up of 180 days, but was 389 days for the 14 patients who received the higher dose of 2×10^8 CAR-Ts/m^2. CRS developed in 4 patients, 3 patients with grade 1, and 1 patient with grade 2 which responded to tocilizumab. Despite promising results, both of these studies are limited by small patient populations and short follow-up times. A phase I trial of CAR T cells specific for CD30 antigen and CCR4 chemokine receptor is ongoing (Table 1).

Histone deacetylases (HDACs) remove an acetyl group from histone proteins, tightening the chromatin structure that wraps around the histones thereby regulating DNA expression, and are implicated in oncogenic pathways [45]. In a phase II trial of heavily pretreated R/R HL patients with a median of 4 prior lines of therapy, treatment with a potent pan-deacetylase inhibitor panobinostat was shown to have tumor reduction in 74% of patients and ORR of 27% including 4% CR [46]. The treatment response was rapid with time to response (TTR) of 2.3 months and median duration of response of 6.9 months. Median PFS was 6.1 months, and estimated 1-year OS was 78%. Panobinostat was well-tolerated with 21% of patients reporting serious drug-related AEs including thrombocytopenia in 9% of patients. Panobinostat has been combined with the ICE regimen in a recent phase II study in which the combination was compared with ICE alone in R/R HL patients [47]. The combination showed an impressive CR rate of 82% compared with 67% without panobinostat, but grade 4 thrombocytopenia and neutropenia

were seen in 100% and 55% of patients, respectively, compared with 33% and 8% in patients who received ICE alone.

Lenalidomide is an immunomodulatory drug (IMiD) which has been shown to have promising activity in multiple hematologic malignancies including multiple myeloma, myelodysplastic syndrome, chronic lymphocytic leukemia, and non-Hodgkin lymphomas. In addition to a direct cytotoxic effect, mechanism of action of lenalidomide includes indirect effects on tumor immunity [48]. Lenalidomide was evaluated in a phase II trial of R/R cHL lymphoma patients with a median of 4 prior lines of therapy and showed a modest ORR of 19% including 1 patient with CR and 6 patients with PR [49]. Lenalidomide was well-tolerated with neutropenia as the most common grade 3 or 4 AE. Lenalidomide in combination with panobinostat did not show increased response (ORR 14%) over the two drugs as monotherapies in the R/R cHL patients [50].

As previously mentioned, a 9p24.1 amplification is frequently seen in HL, leading to upregulation of JAK2, a well-characterized activator of JAK/STAT pathway whose constitutive activation has been shown to be critical in HRS cell proliferation and survival through its effect on HL TME [33, 51]. A potent inhibitor of JAK1/2, ruxolitinib, was evaluated in a phase II trial of R/R HL patients who had a median of 5 prior lines of treatment [52]. Ruxolitinib showed some antitumor activity as a monotherapy with a 9.4% ORR, but the response was not durable with median duration of response of 7.7 months and median PFS of 3.5 months. The drug was fairly well-tolerated, with ruxolitinib-related AEs in 18.2% of the patients and 25 of 40 overall AEs classified as grade 3 or worse. With its limited activity but fair tolerability, ruxolitinib is not an optimal single agent for the treatment of R/R HL but may have a role in combination with other agents.

A selective list of ongoing trials including various other novel approaches with pentamidine (anti-infective drug), ibrutinib (BTK inhibitor), combination of itacitinib (JAK1 inhibitor) and everolimus (mTOR inhibitor), and camidanlumab tesirine (CD25-directed ADC) is shown in Table 1.

Conclusion

The landscape of R/R cHL treatment has changed significantly since the FDA approval of BV. Immunotherapies, targeted agents, and CAR T cell therapies have shown promising results in early phase trials. While further studies with larger populations and longer follow-up times are needed to determine the optimal strategy to maximize cure, they represent a growing list of treatment options that are on the horizon to improve the cure rate and increase duration of remission in multiply relapsed HL patients.

Compliance with Ethical Standards

Conflict of Interest Yun Choi declares that she has no conflict of interest.

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- •• Of major importance

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