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Management of Indolent Lymphoma: Where Are We Now and Where Are We Going

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Summary

Indolent lymphoma comprises a unique and challenging subset of non-Hodgkin lymphoma (NHL). While definitions of indolence will vary, the most common indolent NHL subtypes include follicular lymphoma, marginal zone lymphoma, and small lymphocytic lymphoma. Patients with indolent NHL (iNHL) excluding those with rare localized presentations are often met with an incurable but highly treatable NHL. In the rituximab era, response rates are approaching 90% with rituximab plus chemotherapy and time to next treatment are beginning to be measured in years. As a result of a prolonged natural history, we are encountering a gridlock of novel regimens and agents that appropriately fill peer-reviewed journals. In this review, we tackle a spectrum of topics in the management of indolent lymphoma including the initial approach to the newly diagnosed patient, approaches to first cytotoxic chemotherapy, maintenance and consolidation techniques, as well as highlight promising treatments on the horizon in iNHL. Clinicians continue to face tough choices in the management of iNHL. Through well-thought out clinical trials and peer-reviewed vetting of data we will continue to determine how to best manage the clinical continuum that is iNHL.

Keywords

Indolent lymphoma; Non-Hodgkin; Follicular; Marginal zone; Small lymphocytic; Rituximab; CD20; Cyclophosphamide; Doxorubicin; Bendamustine; Fludarabine; Lenalidomide; Bortezomib; PI3K; mTOR; Bruton’s tyrosine kinase; Histone deacetylase inhibitors

Introduction

The management of indolent non-Hodgkin lymphoma (iNHL) is a test of stamina for both the patient and the practitioner. While crude, the designation of “indolent” describes a behavior that has been assigned over decades of observation with a necessary pause for the uncertainty of individual disease heterogeneity. As noted by the indolent designation, often the natural history of iNHL is measured in years and likely the patient may have lived through many changes in histological nomenclature. For this iNHL review we will focus on important past and present studies in follicular lymphoma (FL), marginal zone lymphoma (MZL), and those that included small lymphocytic lymphoma (SLL).

Collectively, iNHL rivals their aggressive non-Hodgkin lymphoma counterpart in incidence with approximately 22,000 new cases diagnosed each year. [1,2] Pathologically, iNHL represent small to medium lymphocytes arising from discrete lymph node regions with

characteristic immunophenotypic patterns and often low proliferative indices. In the case of FL, the most common iNHL subtype, further histologic grading system has been standardized by Mann and Bérard. [3] Grade 3b FL is treated as an aggressive NHL. The data remains controversial whether it is necessary to treat grade 3a differently than grade 1–2. The median survival of iNHL has surpassed a decade as a multitude of therapies have continued to jockey for position. As treatment paradigms shift, eras end and begin, the volume of literature has become expansive, but with resolve we remain in search of therapeutic strategies that match efficacy with durability and lack short and long term toxicities.

iNHL has a geographic tropism for North America and northern Europe representing 41% of NHL diagnoses compared to 21% in Hong Kong. [4] iNHL continues to be heavily weighted towards whites compared to blacks, but carries gender equivalence. The reasons for geographic and racial separation remain an epidemiologic mystery. The incidence of the diagnosis of iNHL continues to increase. Environmental and lifestyle studies have pointed towards possible risk factors, but remain clinically unsatisfying. Logically, an increase in life expectancy and a surge in use of medical imaging may partly reflect this increased incidence. The later point continues to confound treatment strategies in iNHL as lead-time bias remains a paramount confounder in management.

Strategies to predict survival based upon disease characteristics at diagnosis in iNHL were completed both in the pre-rituximab and post-rituximab era. The international prognostic index (IPI), which had been validated for survival in aggressive lymphoma, was also predictive in iNHL, but was unable to distribute risk factors effectively and led to inferior prognostication. [5] Therefore, the follicular lymphoma international predictive index (FLIPI) was created for FL, but has applicability in both MZL and SLL. [6] The FLIPI employs the core risk factors of the IPI age > 60, Ann-Arbor stage ≥ 3, and an elevated lactate dehydrogenase (LDH) value, but substitutes the hemoglobin value of < 12.0 g/dL and number of nodal sites ≥ 5 are singularly and collectively important predictors of survival. (See Table 1) Clinically, the FLIPI can be used descriptively to help compare an individual patient to those with similar FLIPI scores. However, the FLIPI was retrospective and manifests a patient population in the pre-rituximab era. More importantly, the FLIPI allows for clinical trial interpretation of results especially in the rituximab-chemotherapy era. [7] A second FLIPI, known as the FLIPI2 prospectively analyzed patients with FL in the rituximab era. The FLIPI2 removed the often difficult calculation of number of nodal sites (as it is different than the Ann-Arbor nodal groups) and applied the longest diameter of the largest involved lymph node > 6 cm, bone marrow involvement, and B2 microglobulin > upper limit of normal as risk factors (See Table 1). [8] These results revalidated the FLIPI prognostic concept with rituximab plus chemotherapy (R-chemo) by progression free survival (PFS). The FLIPI or FLIPI2 scores do not provide guidance towards the immediacy or type of the treatment that should be given in the setting of iNHL. Therefore, in this review we will tackle aspects of the treatment of advanced stage and relapsed iNHL reviewing where we are now and highlight where we were are going.

Management: Where Are We Now

The initial diagnosis of an iNHL is an opportunity to learn as much about the patient and his or her beliefs as much as it is about the disease. The vast majority of patients will present with advanced (stage III-IV) Ann-Arbor stage disease, but are often asymptomatic. Not infrequently, the crux of many conversations is whether to treat or not to treat at the time of diagnosis. Patient preferences and the literature often guide these trepid encounters.

Watch and wait

Historic single institution studies [9,10] and three prospective studies have given credence to an initial watch and wait approach in iNHL in the pre-rituximab era. Brice et al. first investigated a watch and wait approach in a three arm study involving low tumor burden FL. [11] The watch and wait approach challenged two therapeutic strategies, an oral alkylating agent prednimustine and the immune directed therapy interferon alpha. The results demonstrated that deferring treatment did not influence survival at 5 years. However, in all groups those who progressed in the first year had a significantly shorter median survival of 4 years. Shortly thereafter Young et al. proposed that intensive chemotherapy with ProMACE-MOPP (cyclophosphamide, doxorubicin, etoposide, cytarabine, bleomycin, vincristine, methotrexate with leucovorin, and prednisolone) compared to watchful waiting approach would improve overall survival. [12] Unfortunately, the intense regimen did not improve overall survival at five years. Ardeshna et al. then reconfirmed the watch and wait strategy compared to oral chlorambucil, another alkylating chemotherapy agent. [13] Those patients in the watch and wait cohort had a longer median survival of 6.7 years compared to 5.9 years in the chlorambucil arm. At ten years, 19% of the patients in the watch and wait cohort had not required therapy, however, 6% had pass away from non-lymphoma etiologies.

In the Ardeshna manuscript the disease related exclusion criteria in this study later evolved to be known at the National British Lymphoma Investigation (NBLI) guidelines for patients who should not be consider for a watch and wait approach (See Table 2). Similarly, a slightly different strategy was propose by the Groupe d'Etude des Lymphomes de Adulte (GELA) who accrued only advanced stage FL patients who were allowed to enrolled if any advanced disease criteria were met. These criteria are now known as the Groupe d'Etude des lymphomes folliculaires (GELF) criteria (see Table 2) have to date influenced and attempted to dichotomize the timing of initiation of therapy in advanced iNHL. Commonly, the GELF criteria are used as modern eligibility criteria in clinical trials clearly overshadowing the results of the GELF 98 trial that they arose from. [14]

Single agent immunotherapy

Leading up to the discovery of antibodies towards CD20 on malignant B lymphocytes, cytotoxic chemotherapy cocktails had made unimpressive dents into the Kaplan-Meier curves of patients with iNHL. The CD20 monoclonal antibody rituximab (R) (MabThera/Rituxan) (Roche and Genentech) ushered in a new era in the treatment of iNHL. The phase I studies demonstrated no dose limiting toxicities at a single dose of 500mg/m^2 and a tolerable weekly dose schedule of 375 mg/m^2 for 4 treatments. [15,16] Both early phase studies hinted towards efficacy in iNHL with responses seen regardless of the location of lymphoma. The initial phase II study of rituximab in a chemorefractory patient population demonstrated surprising single agent efficacy with an overall response rate of 46%. [17] Subsequent confirmatory phase II studies by a multi-center international consortium and the German low-grade lymphoma study group (GLSG) reported an overall response rate (ORR) of 48% and 47% respectively using the weekly dosing strategy. The median time to progression was 13 and 7 months respectfully, but also highlighted poor responses in those patients who had bone marrow involvement, but not necessarily bulky disease. [18–20] Rituximab received FDA approval for the treatment of relapsed and refractory low-grade or follicular lymphoma, B cell NHL on November 26th, 1997.

Given the single agent activity in the relapsed or refractory population rituximab was studied in the untreated iNHL population. In two small studies, patients with low disease burden advance stage iNHL rituximab were administered at 375 mg/m^2 weekly doses for 4 weeks cycles. [21,22]The ORR after one cycle was 47% and 73%. In a similar break-out study, Hainesworth et al. treated patients with SLL/CLL with an ORR of 51% after one cycle of

rituximab. [23] These results led to a randomized study by Ardeshna and colleagues designed to challenge the watch and wait paradigm that nearly a decade early had overcome challenges from both low toxicity oral chemotherapy to high intensity systemic combination chemotherapy. In this three armed study patients with advanced low burden disease without meeting any GELF characteristic received either watchful waiting, rituximab monotherapy as the standard four weekly doses for 1 cycle, or one standard induction dose followed by maintenance rituximab given every 2 months. [24] Arm B was closed early given the promising results seen with maintenance therapy (see maintenance strategy section). The primary endpoint of the study was time to first therapy defined as chemotherapy or radiation therapy. At first scheduled analysis (7-months post randomization) the rituximab single agent plus maintenance therapy had achieved an ORR of 85% with 39% obtaining a complete remission (CR) while in the watch and wait arm only 3% had progressive disease. The median time to first chemotherapy in the watch and wait arm was 33 months, which was comparable to previous historical reports. In either arm with single agent rituximab and rituximab plus maintenance neither the median time to first chemotherapy has yet to be reached at 4 years. Importantly, only 59% of the patients who had demonstrated progressive disease have required therapy. At the time of this report 98% of the patients enrolled were alive denoting the clear infancy of the report, but regardless thought provoking results. As a result, rituximab therapy for patients with newly diagnosed disease without GELF criteria is now a potential topic for discussion for those who do not feel comfortable with a watch and wait approach.

Combination chemoimmunotherapy

The success of the rituximab as a single agent in the relapse setting also led to a global explosion of clinical trials. As described above, patients at select centers were offered single agent rituximab. Other centers added rituximab to a multitude of active combination chemotherapy backbones. The evidence for prior activity of historic non-rituximab iNHL regimens was eloquently described in a 2005 Blood Review by Gandhi and Marcus and will be selectively discussed in this review. [25] We will further review the role that rituximab has had in addition to combination chemotherapy chemotherapies.

In the infancy of rituximab development Czuczman and colleagues pioneered the use of rituximab in combination with multidrug chemotherapy, in this case cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) in iNHL. [26] Previously treated and newly diagnosed patients with measurable iNHL received 6 cycles of R-CHOP. They reported a 100% ORR (2 initially included didn't receive therapy and were considered non-responders in initial intent to treat analysis) with 87% achieving either a CR or an unconfirmed complete response (CRu). The median time to progression and duration of response was 82.3 and 83.5 months respectively. The study defined disease specific criteria for enrollment as measurable disease < 10 cm in either the relapsed or untreated patient population. A slightly different administration of rituximab was used in this report with rituximab given on days 1, 7, 48, 90, 134, and 141. [27] Building on the phase II activity in iNHL and an eye on the successes of R-CHOP in aggressive NHL a subsequent phase III study was performed by the GLSG comparing the efficacy of CHOP to R-CHOP in advance stage grade I–II FL with pre-defined criteria for treatment eligibility. [28] The study concretely displayed the superiority of R-CHOP in all measures including ORR, time to treatment failure, and duration of remission. However, the six cycles of rituximab were combined with the administration of CHOP unlike what Czuczman et al had previously proposed.

Simultaneously, other groups were investigating non-anthracycline based regimens demonstrating the continued diversity of up front management of iNHL. The regimen of eight cycles of cyclophosphamide, vincristine, and prednisone (CVP) was compared to the

addition of rituximab (R-CVP) in a phase III study. [29] As seen with R-CHOP, R-CVP dominated the non-rituximab treatment arm with significant improvements in ORR (81%) and CR rates (41%). Furthermore, the time to progression was doubled (30 months) in the R-CVP arm. A later publication highlighted the significant durability of R-CVP with 53-month median follow-up a time to progression of 34 month and duration of response of 38 months. [30] Moreover, with the application of the then validated FLIPI score noted that all categories of the FLIPI remained statistically significant in favor of R-CVP in post hoc analysis.

Fludarabine is a potent purine analog that had shown significant activity as a single agent and also when combined with other cytotoxic agents in iNHL. [31–36] Single agent fludarabine activity was compared with CVP in a phase III study in the pre-rituximab era with fludarabine demonstrating a superior CR rate of 38.6% compared to a 15% in the CVP arm in newly diagnosed advanced stage iNHL. Fludarabine was associated with more grade 3–4 hematologic toxicities, but this did not translate in to more infections. [37] A randomized phase II studying fludarabine and cyclophosphamide with or without rituximab (FC/FCR) in iNHL reported significant prolonged thrombocytopenia in 35% of the FCR treated patients resulting in early discontinuation of the study. [38] However, this regimen was redeemed with the report of the fludarabine, cyclophosphamide, mitoxantrone, with or without rituximab (FCMR) that did not encounter prolonged thrombocytopenia likely as a result of dose and scheduling manipulations and demonstrating improved efficacy with the inclusion of rituximab in relapsed iNHL. [39] Fludarabine containing regimens, FR, FCR, and FCRM continue to be an attractive option for the upfront management of indolent lymphoma; however, the recent publication from the PRIMA study demonstrated only 4% of the patients receiving a fludarabine based regimen as initial treatment. [40] Another clinical caveat in regards to fludarabine-based regimens is if considering consolidative autologous transplantation mobilization of progenitor cells after fludarabine regimens has been met with significant challenges. [41]

Bendamustine is a relatively old chemotherapeutic agent with a novel structure thought to combine the assets of an alkylating compound (nitrogen mustard) and a purine analog (benzimidazole ring). Much of efficacy and utility of bendamustine had been hidden for decades behind the iron curtain of the former East Germany. Two years after the unification of Germany bendamustine began to appear into the peer-reviewed literature. Early reports publicized the activity of bendamustine in iNHL. [42] Nearly a decade later a third German phase II single agent study demonstrated the single agent ORR of 73% with 11% achieving a CR with bendamustine administered at 120 mg/m^2 for two consecutive days. The median number of treatments to achieve a persistent response (two response intervals) was six with duration of response of 16 months. [43] Later, in a similar patient population bendamustine was partnered with rituximab (BR) with a dose reduction to 90 mg/m^2 in 47 patients with iNHL eliciting an impressive response rate of 96% with a much improved CR rate of 64%. [44] Myelosuppression remained the major toxicity seen with BR whereas thrombocytopenia was a rare event. These promising results led to the much-touted phase III study pitting BR versus R-CHOP in iNHL. Mantle cell lymphoma (MCL) is included in this discussion as the peer-reviewed manuscript has yet to be published, but regardless included in this review given the potential practice changing results. The 549 patients reported in the abstract had similar disease characteristics and all were in need of treatment by pre-defined criteria. [45] With a median of 32 months of follow-up the ORR were similar (BR--93.8% vs R-CHOP--93.5%), but CR, PFS, and time to next treatment were significantly higher and longer in the BR cohort. Surprisingly, there was a significant difference in grade 3–4 toxicities favoring BR and increased use of growth factor support in the R-CHOP cohort. Interestingly, despite the unpublished nature of the abstract at ASH 2011 the National LymphoCare study reported that community based practices had already transitioned

towards the BR despite compelling evidence towards the uniformity of response to R-CHOP, R-CVP, and an R-fludarabine based regimens. [46]

A resulting meta-analysis searching all trials from 1990 to 2005 comparing non rituximab containing regimens in those with newly or relapsed indolent lymphoma to confirmed the overall survival (OS) superiority of the R-chemo regimens. [47] The analysis included 1943 patients with iNHL. In their analysis R-chemo was associated with a 65% risk deduction of death due to lymphoma with superior initial response and duration of response. These results hammered the nail in the coffin of non-rituximab containing regimens and prompted early development of phase IIa combination regimens with the inclusion of rituximab.

Consolidation and maintenance strategies

iNHL in general invariably relapses after initial therapy is administered and chemosensitive disease is established. This duration of response is variable but for most it is measured in years not months. Therefore, iNHL has long been considered an incurable but highly treatable condition. In the era of rituximab, primary refractory indolent lymphoma is uncommon, but when encountered consolidative and maintenance strategies are of less utility until chemosensitivity is re-established. In those who have chemotherapy, immunotherapy or chemoimmunotherapy sensitive disease at any point in their treatment continuum have often been considered for consolidative or maintenance strategies with the goal of provided effective therapy with low risk toxicities with the hope of delaying the relapse and prolonging the time to next treatment. Different strategies have been attempted in this setting including the consolidation with radioimmunotherapy (RIT), maintenance strategy of intermittent use of immunotherapy, and autologous and allogeneic stem cell transplantation.

RIT targeting CD20 with either ^{131}I tositumomab or ^{90}Y ibritumomab tiuxetan have been investigated in the single agent up front and combination chemotherapy setting, as a single agent in the relapse/refractory population, and as a conduit to autologous stem cell transplantation. A recent consensus paper helps guide clinicians in regards to the idiosyncrasies of RIT administration and is beyond the scope of this review. [48] RIT in the consolidative stage of the management in iNHL targets residual lymphoma as expressed as a function of depleting CD20 positive lymphocytes with either β or γ radiation particles with the additional benefit of resulting in collateral damage to those lymphocytes that may have acquired immunoresistance by down regulating and eventual lack of surface expression of the CD20 receptor. However, the radiation induced collateral damage is not limited to malignant lymphocytes, but other cell lineages resulting in neutropenia, thrombocytopenia, and the risk of development of myelofibrosis. Therefore, patients have to be carefully selected if RIT is to be used effectively as consolidation after R-chemo. Initial consolidation data in the first line setting using CHOP for 6 cycles followed by consolidation with ^{131}I tositumomab demonstrated a 91% ORR in advanced iNHL. [49] Further investigation with initial consolidation with ^{131}I tositumomab in untreated iNHL employed the non-anthracycline based regimen of CVP with similar results of a 100% ORR with 93% obtaining a CR. With a median of 8.4 years the median duration of response has yet to be reached, but five-year OS was 83% with 56% percent progression free. Both results were encouraging and led to the phase III intergroup study of upfront CHOP followed by ^{131}I tositumomab consolidation versus standard R-CHOP in untreated patients with FL. The results presented in 2011 at ASH demonstrated no significant differences in ORR, CR rate, and 2-year PFS. [50] The toxicity outcomes were also similar between cohorts. Notably, the R-CHOP regimen used a rituximab-based schedule that had previously been published by Czuczman and colleagues. [26] These results may limit the use of RIT in the future given the fairly complex administration and scheduling and again affirms the necessity of randomized phase III trials regardless of the nature of the lymphoma. Nevertheless, a phase

II trial using both consolidative I^{131} tositumomab as well as rituximab maintenance therapy (ala PRMIA) on the backbone of R-CHOP has been fully accrued and results are pending (Table 3).

Maintenance strategies with rituximab were envisioned from the initial use of rituximab in both untreated and previously treated iNHL patients. It has been attempted with success in both patients who received single agent rituximab and rituximab and combination chemotherapy. [51,52] To add to the complexity of maintenance therapy, rituximab was delivered at differing time points including every two, three, and six months. [52–55] Regardless of the delivery schedule, all regimens demonstrated the ability for rituximab maintenance therapy to yield impressive PFS data and, while rare, conversion of partial responses to complete responses. Importantly, the phase III PRIMA study provided some clarity to the maintenance question following a rituximab based chemotherapy induction and utilizing the maintenance schedule from the EORTC 20981 study for patients with GELF criteria disease whom were diagnosed within 4 months. [40] Those who had achieved a chemosensitive disease state defined as at least a PR were randomized to rituximab every 3 months for a 2-year maintenance strategy or standard expectant radiographic observation. Notably, this study excluded those who may have initially been observed and then had progressive GELF criteria disease. At a median follow-up of 3 years the PFS was 57.6% in the observation arm and 74.9% in the rituximab maintenance arm. There was no overall survival advantage for the maintenance arm. Patients who received maintenance therapy were also more likely to be in remission at the end of the maintenance therapy. As a tradeoff for being in remission, grade 2–4 infections were seen more often in the rituximab maintenance arm. The National LymphoCare Project provided evidence that the oncologic community has embraced the PRIMA maintenance strategy despite the lack of survival advantage. [56] Subsequently, rituximab maintenance following an R-chemo approach appears to be feasible for those who are deemed to require therapy at presentation, but the endpoint of improvement of OS remains an elusive yet important endpoint in iNHL.

The same cannot be said to be true for those patients with newly diagnosed low disease burden (no GELF criteria) iNHL who receive rituximab monotherapy as the initial therapy. The RESORT trial investigated in a randomized fashion the use of single agent rituximab in a standard weekly for 4 treatments followed by observation and retreatment with single agent rituximab again at time of radiographic evidence of relapse versus every 3 months rituximab maintenance following single agent induction. [57] The primary endpoint of this study was time to treatment failure. An event was defined as progression less than 6 month from the last dose of rituximab, no response to rituximab retreatment, initiation of an alternative treatment, and inability to complete the prescribed protocol. The outcomes of the RESORT trial was presented by Kahl and colleagues at ASH 2011 demonstrating the lack of improvement with maintenance rituximab in regards to the primary endpoint of time to treatment failure. However, maintenance rituximab did prolong the time to first chemotherapy, but at the expense of three times more rituximab having to be administered. Interestingly, health care quality of life was not different between groups in regards to anxiety. Anecdotally, both arms prolonged time to first chemotherapy when compared to historical watchful waiting studies (see Watch and Wait section). In the end, this may have a been a missed opportunity to include a watchful and wait arm to bring further clarity to the upfront management of iNHL as these patients had low burden disease and were not required to meet GELF criteria to enroll as they had been in the PRIMA study. Furthermore, these results will make the interpretation of the Intergroup study comparing watchful waiting to rituximab therapy with maintenance as they chose to close the no maintenance arm of the study. [24] Lastly, an important disease characteristic which will branch from this study will be how these patients will respond to the initial chemotherapy based therapy with rituximab and whether their response rates drops and returns to the pre-rituximab era.

Stem cell transplantation: Autologous and Allogeneic

Autologous stem cell transplantation has been extensively studied in iNHL as a consolidation strategy for chemosensitive indolent disease either after induction therapy or relapsed disease. [58–68] Many of these studies demonstrated a significant improvement in PFS compared to historical controls. Furthermore, it has been conclusively shown that the timing of autologous stem cell transplant matters in the course of iNHL. [69] Patients obtain the most benefit if the consolidative autologous transplantation is performed prior to the third cytotoxic regimen. The single agent treatment with rituximab does not appear to have counted as a cytotoxic treatment regimen. A high-risk FLIPI and histologic grade 3a follicular lymphoma were also factor that predicted worse outcomes.

Randomized prospective studies for consolidation with autologous stem cell transplantation are limited. The chemotherapy vs. unpurged stem cell transplant vs. purged transplant (CUP) trial was a randomized phase III trial of induction chemotherapy with CHOP for three cycles followed by high dose therapy and autologous stem cell transplantation or completion of induction chemotherapy for a total of six cycles. [70] In the 89 patients who completed randomization (64%) PFS was significantly prolonged in those who underwent transplantation. The four-year overall survival was 46% in the untransplanted cohort and nearly 75% in the transplanted cohort with a trend towards a survival advantage (p=0.079). Whether or not the stem cells were purged in the transplant arm did not factor into the outcome. Ladetto and colleagues reported upfront autologous stem cell transplantation outcomes in the rituximab era using a CHOP induction backbone followed by four treatments of rituximab and peritransplant rituximab maintenance. [71] While a greater CR rate (85%) and prolonged event free survival was seen in those patients who were randomized to consolidative high dose therapy with autologous stem cell rescue they were unable to demonstrate an OS advantage. These results perhaps display that in the rituximab era administering rituximab with induction and salvage chemotherapy may overcome the percentage of patients that would be salvaged by high dose therapy and autologous stem cell transplantation.

Direct randomized comparisons of autologous to allogeneic stem cell transplantations do not exist in iNHL. Early studies of allogeneic transplantation were single center reports of outcomes using mostly myeloablative total body irradiation preparative regimens. [72–74] A large registry based retrospective review of 904 patients who either received an autologous or allogeneic transplantation demonstrated significant insight. [75] While only 19% had undergone an allogeneic transplantation for follicular lymphoma the 5-year treatment-related mortality was 30% compared to 22% in the purged and unpurged autologous transplant cohort. The 5-year recurrence rates were 21% in the allogeneic cohort and 43% and 58% in the purged and unpurged autologous transplantation cohorts respectively. Total body irradiation was associated with higher transplant related mortality but a lower recurrence rate. More recently, select centers have chosen to explore reduced intensity preparative regimens in multiply relapsed iNHL. [76–78] (see Table 3) The reduction of the conditioning intensity is designed to exploit the graft-versus-lymphoma effect and decrease transplant related mortality. Khouri and colleagues reported an eight year experience with the reduced intensity regimen of fludarabine, cyclophosphamide and rituximab in 47 chemosensitive relapsed patients. [79] Only two of the 47 patients had relapsed after a median follow up of 5 years. They also reported an 11% grade II–IV graft versus host disease with 11% of the patient on continued immunosuppression. An update of their data to 12 years (median follow-up 9 years) demonstrated continued success with only one further patient having relapsed, and an 11-year PFS and OS of 78% and 72% respectively. The manuscript also included the initial report of the planned substitution of ^{90}Y ibritumomab tiuxetan for rituximab to the reduced intensity regimen for those with chemorefractory disease. In the 26 patients treated 14 had chemorefractory disease and would have

previously been excluded from reduced intensity transplantation. [80] With a median follow-up of nearly 3 years the 3-year PFS of those with chemorefractory and chemosensitive disease was 80% and 87% demonstrating promising results in an otherwise difficult patient population. While allogeneic stem cell transplantation has had significant advances with reduced intensity transplantation further strategies are moving to attempt to decrease the amount of GVHD that is seen without decreasing efficacy. Furthermore, measures either serologic or pathologic to predict in relapsed iNHL patients who would benefit from allogeneic transplantation earlier in the course of therapy remains an ongoing area of research.

Management: Where Are We Going?

In the twenty-first century a rituximab based approach with or without combination chemotherapy has fundamentally changed the natural history of iNHL. Nonetheless, relapse is invariable and in many rituximab refractory disease is inevitable. Furthermore, subsequent combination cytotoxic treatments are compounded by shortened disease free intervals and cumulative intensity limiting toxicities. Novel agents steering away from the indiscriminate cytotoxic dogma are needed. Herein, we review classes of agents, which have shown potential efficacy as single agents and where available in combinations in relapsed iNHL.

Proteasome Inhibitors

Bortezomib is the first proteasome inhibitor to see extensive use in relapsed iNHL. Bortezomib has demonstrated significant clinical activity warranting FDA approval in previously treated multiple myeloma and mantle cell lymphoma. Single agent activity in relapsed iNHL using similar dosing strategies with variable efficacy has been demonstrated. [81–83] Akin to the development of bortezomib in multiple myeloma several dosing and schedule strategies were explored to maximize efficacy while minimizing toxicity. In a phase II study, patients with relapsed iNHL were treated with rituximab (375 mg/m2) given weekly for 4 doses and bortezomib at either 1.3 mg/m^2 twice weekly (days 1, 4, 8, and 11) of a 21-day cycle for 5 cycles or 1.6 mg/m^2 weekly (days 1, 8, 15, and 22) of a 35-day cycle for 3 cycles. [83] The ORR was comparable with the biweekly regimen at 49% and 43% for the weekly regimen. The weekly regimen was found to be less toxic. However, other groups have demonstrated inferior activity of the weekly regimen when compared to the biweekly administration, but confirmed better tolerance. [84] Nonetheless, the weekly regimen plus rituximab was studied in a randomized phase III study in rituximab-naïve or rituximab sensitive FL grade 1–2. [85] In the standard arm patients were given weekly rituximab for 4 treatments in cycle 1 with subsequent rituximab on day 1 of each successive cycle. Patient randomized to the experimental arm received bortezomib 1.6 mg/m^2 weekly (days 1, 8, 15, and 22) of a 35-day cycle and rituximab as above. After a median follow-up of nearly 3-years the median progression free survival favored the combination therapy (11.0 vs. 12.8 months; p=0.039). However, the pre-specified improvement of progression free survival of 33% was not met. Furthermore, the bortezomib containing arm had more than twice as many grade 3 or greater toxicities with nearly one in five patients experiencing peripheral neuropathy (3% grade ≥ 3). Rituximab-bortezomib has been safely combined bendamustine given at 90 mg/m^2. [86] Further analysis of the dose escalation phase II VERTICAL trial with weekly bortezomib trial demonstrated an impressive ORR of 88% with 53% achieving a CR; however, the study failed to achieve the primary endpoint of a 60% complete response. [87] The median duration of response was 11.7 months with the median number of rituximab and cytotoxic treatments of two. Nearly half of the patients were refractory to the last R-chemo regimen. Peripheral neuropathy remained an issue with grade 3 or greater neurotoxicity of 11%. A similar yet competing multicenter phase II trial utilized the twice weekly bortezomib, rituximab, and bendamustine with an impressive 93% ORR in iNHL. [88] Peripheral neuropathy remained present with 47% experiencing grade 1–2 toxicity;

however only 2 patients had grade 3 neuropathy. This regimen is now accruing patients as part of randomized trials to evaluate this regimen in iNHL (Table 3). Other groups have also continued to explore the bi-weekly bortezomib-rituximab in a rational fashion by including or substituting bortezomib for vincristine in the known effective R-CVP regimen in untreated and relapsed iNHL. [84,89] The biweekly regimen was well tolerated with an ORR of 83% in untreated patients in a phase II study and 64% in a phase I study. Hopefully, open and accruing protocols will adapt a subcutaneous approach to improve the tolerability of these regimens in a relapsed and palliative patient population. Second generation proteasome inhibitors MLN-97 and carfilzomib remain in early phase development in hematologic malignancies.

Immunomodulatory Agents

The microenvironment surrounding foci of iNHL is complex and only recently patterns are becoming clinically useful. [90] Targeting the microenvironmental meshwork through immunomodulation was initially attempted with thalidomide in iNHL with lack luster results. [91] Lenalidomide a second-generation immunomodulatory (IMiD) with unclear mechanisms of action, but is felt to be a stronger immunomodulatory agent than thalidomide with a safer side effect profile. Lenalidomide was found to be efficacious in myelodysplastic syndrome and previously treated multiple myeloma resulting in FDA approval. Lenalidomide has also been studied in CLL and aggressive lymphoma with encouraging results. [92,93] Witzig and colleagues presented the initial single agent study of lenalidomide in iNHL. [94] The oral pill taken daily for 21-days of a 28 day cycle resulted in an ORR of 23% with 7% complete responses. Surprisingly, the median duration of response was not reached and was longer than 16.5 months in 7 of 10 responders. Logically, these results led to the combination of lenalidomide with rituximab. Nearly simultaneously two groups reported results in untreated and relapsed iNHL. In the relapsed population Dutia and colleagues used standard lenalidomide at 25 mg orally for 21days followed by rituximab starting at day 15 for four weekly doses with repeat rituximab optional depending upon response. [95] In the 12 evaluable patients, 10 (83.3%) had a response with 4 patients achieving a CR (33%). Notably, responses were seen in 66% (4/6) patients with previously rituximab refractory disease. Fowler and colleagues studied patients with measureable (>1.5 cm) iNHL who had not received iNHL specific therapy using a different dosing strategy with rituximab (day1) and lenalidomide (days 1–21) for six cycles. [96] Their results also were quite impressive with 86% of the patient with at least a PR and 65% obtaining a CR. Specifically in FL 94% obtained a CR. The median follow-up was 14.1 months with only one patient experiencing progression of disease. Further data using this strategy was then expanded to include those patients who were untreated and GELF criteria disease (54%) and their results continued to be impressive with an ORR of 90% with 66% achieving a CR. [97] Responses were high regardless of FLIPI score or GELF criteria at time of treatment. Side effects remained manageable with skin rash and deep venous thrombosis the most common non-hematologic toxicities. Neutropenia was seen in 27% of the patients. Both single institution results prompted a randomized phase II study of lenalidomide versus rituximab plus lenalidomide in a relapsed iNHL (CALGB 50401). [98] A rituximab only arm was attempted but was closed due to slow accrual. The rituximab was given weekly for four doses and not repeated. Lenalidomide was given initially as 15 mg daily then escalated to 20 mg after the rituximab was completed. In the 89 patients (45 lenalidomide alone and 44 lenalidomide plus rituximab) the ORR was 49% in the lenalidomide alone arm and 75% in the combination. With a median follow-up of 1.5 years the median event free survival was 1.2 years and 2 years in the lenalidomide arm and combination arm respectively. These results point towards a superiority in the combination arm in relapsed iNHL. Lastly, the lenalidomide plus rituximab is planned to challenge R-chemo in a head to head international phase III trial in FL in patients who meet GELF criteria now known as the RELEVANCE

trial (Table 3). A caveat to this study is that patients in this study will be able to have been previously monitored without treatment unlike the PRIMA study, which required enrollment within 4 months of diagnosis. Interestingly, both maintenance rituximab and lenalidomide are planned components of this trial. While this protocol will likely to take years to accrue and nearly a decade to obtain meaningful results we applaud the iNHL community for attempting to foresee where we are going despite lack of treatment uniformity in the upfront setting.

Intracellular pathway targeting agents

The B-cell receptor (BCR) signaling pathway is intricately involved in lymphomagenesis. Several downstream kinases are augmented in the malignant B-cell leading to malignant proliferation. The first and most upstream kinase from the BCR that has been clinical evaluated was the spleen tyrosine kinase (SYK). Fostamatinib, an inhibitor of SYK was also explored in rheumatic diseases and was well tolerated. In a phase II study, Friedberg and colleagues demonstrated adequate non-hematologic tolerability, but nearly one-third of the patients experienced grade 3–4 neutropenia. [99] Fostamatinib lacked significant activity in FL with an ORR of 9.5% and a short median PFS of 4.5 months; however, it was quite active in CLL where over half of the patients experienced a PR. Fostamatinib has yet to be further developed in iNHL, but remains a possible agent for novel biologic combinations. Further downstream is the Bruton's tyrosine kinase (BTK), a specific kinase important to B-cell maturation that interestingly has not been shown to be present in the T-cell receptor kinase repertoire unlike SYK. BTK inhibition leads to B-cell apoptosis *in vitro* and *in vivo* lymphoma models. Ibrutinib (PCI-32765) is a novel oral irreversible inhibitor of BTK at a distinct cysteine residue. The phase I study demonstrated significant single agent activity with an ORR of 42% in the iNHL subtypes studied. [100] Notably, responses were seen regardless of dose cohort and importantly no long-term toxicity has been seen. A phase II study in relapsed SLL/CLL demonstrated a 44% response rate with responses seen regardless of cytogenetic abnormalities pre-treatment. [101] Recently, ibrutinib was further studied in SLL/CLL treatment naïve patients with an ORR of 73% with an 8% complete response rate. The oral medication remains well tolerated without significant hematologic toxicities and manageable non-hematology toxicities. [102] Phase II study in aggressive NHL are accruing with excitement; however discrete phase II studies in FL or other iNHL are still in development (Table 3).

Phosphatidylinositol 3-kinase (PI3K) and mammalian target of rapamycin (mTOR) are important proteins involved in cellular metabolism and dysregulation of expression has been shown to be lymphomagenic. PI3K inhibitors are earlier in development than mTOR inhibitors, which had a significant lead time use in solid tumor oncology. PI3K has several important physiologic isoforms (α, β, δ, and γ) with hematopoietic importance being demonstrated in both the δ and γ isoforms. The former has a discrete p100 isoform, which has been shown to be important in B-cell proliferation. Multiple δ inhibitors are in development, but GS-1101 (the drug formerly known as CAL-101) has been extensively developed in CLL and is currently undergoing testing in phase III studies. In iNHL Kahl and colleagues reported impressive single agent response rates in the relapsed cohort with an ORR of 62% (including 3 patients with Waldenström's macroglobulinemia). [103] Again, as with the BTK inhibitor ibrutinib, responses were seen in multiple dose levels with low-grade non-hematologic and hematologic toxicities of unclear association to the GS-1101. Further strategies in iNHL with GS-1101 as a single agent and with combination chemotherapy are ongoing. [104] (Table 3). mTOR is a family of proteins that is distal to PI3K (PTEN) activity. mTOR inhibitors have been in used in hematologic transplantation medicine for years given the ability to dampen T-cell responses and therefore mitigate the risk of graft versus host disease. There are several mTOR inhibitors in oncologic development with

everolimus (RAD-001) leading the investigation in both aggressive and iNHL (Table 3). [105] In a phase II study of everolimus taken orally at 10 mg daily (option to decrease to 5 mg) in 145 evaluable patients had an ORR of 33% with 8 patients (50%) with FL deriving an objective benefit. [106] Dual PI3K and mTOR inhibitors are in pre-clinical evaluation and have demonstrated activity in iNHL cell lines. [107]

Apoptosis-targeting agents

Cellular apoptosis in a benign lymphocyte is a common event. The apoptotic pathway is well regulated with a system of checks and balances with two branches: the extrinsic pathway driven by tumor necrosis factors and the intrinsic pathway with the master regulator B-cell lymphoma-2 (BCL-2) protein super-family occupying the mitochondria. Rather than cause proliferation the role of BCL-2 super-family is to prevent or promote apoptosis. Characteristic of FL is the t(14;18) cytogenetic abnormality leading to BCL-2 gene overexpression and results in elevated protein levels inhibiting cytochrome C release (i.e. apoptosis) in the mitochondria. Therefore, agents targeting BCL-2 anti-apoptosis proteins, inhibitors of apoptosis, or enhancers of apoptosis remain attractive and are in development (Table 3). Navitoclax (ABT-263) is a potent oral BCL-2 inhibitor with high affinity for multiple anti-apoptotic BCL-2 related proteins (Bcl-X_L, Bcl-2, Bcl-w, and Bcl-B) and efficacy in lymphoma cell lines. In a phase I study two dosing strategies were tested in a dose escalation modified 3+3 design. In group one, patients were dose escalated on a platform of 14 days on 7 days off of a 21-day cycle and group two had continuous dosing for a 21-day cycle. [108] In the end, a 150 mg 7-day dose lead-in then escalation to 325 mg daily for 21 days was chosen for phase II studies. In this study, responses were seen in 10 patients and SLL/CLL patients appeared to derive the largest benefit; however, this agent is planned for broad phase II development. Other apoptotic pathway targeting agents earlier in development include obatoclax, YM155, and AT-101.

Epigenetic modulators

Epigenetics refers to modulation of gene expression without alterations in the DNA sequence. There are two interconnected mechanisms of epigenetic modulation, which have been well vetted: covalent chromatin alteration by acetylation and methylation of DNA. A host of cellular targets and processes are thought to have suffered malignant epigenetic assaults including angiogenesis, apoptosis, cell cycle, and the tumor microenvironment. Histone deacetylase (HDAC) inhibitors have shown activity initially in cutaneous T-cell lymphoma leading to FDA approval in the relapsed setting and later in peripheral T-cell lymphoma. [109,110] Vorinostat, an oral HDAC inhibitor has demonstrated an acceptable toxicity profile and an early efficacy signal in B-cell lymphoma. [111,112] The phase II study of vorinostat in relapsed or refractory B-cell lymphoma demonstrated an ORR of 29%, which was elevated to 40% with removal of MCL patients. [113] Vorinostat has moved into combination therapy in further study and outcomes are pending (Table 3). Unfortunately, the outcomes for the DNA hypomethylating agent decitabine did not fared as well. In a phase I study of low-dose decitabine (15 mg/m^2 days 1–5) in relapsed CLL and NHL, 4 of 6 patients experienced a dose limiting toxicity including grade 3–4 neutropenia, thrombocytopenia, and neutropenic fever. [114] Furthermore, there was evidence of lack of target hypomethylation in patient samples. These early results will likely hamper, but not exclude, further development of hypomethylating agents in iNHL.

Conclusion

In the pre-rituximab era cytotoxic agents have flexed their muscle yielding respectable clinical response rates, but went flaccid with inevitable relapses without a benefit in OS. The emergence of rituximab salvaged a majority of these patients, but currently it is difficult to

imagine a patient who will not have received rituximab at time of first treatment and relapse(s). Therefore, rituximab refractory iNHL is in the clinic today and will remain for the foreseeable future. As a result, an era targeting further extension of the natural history of iNHL will be difficult, but well-designed phase III are planned and accruing. In the relapsed setting we remain perplexed regarding who should be offered an autologous or allogeneic stem cell transplantation as the list of novel targeted therapies lengthens and responses encroach upon combination chemotherapy, but the durability remains unreliable. Thankfully, encouraging data exist for preliminary success in chemorefractory patients with novel RIT conditioning strategies, but this data needs further multi-center validation. The novel agents of lenalidomide and bortezomib are appropriately moving forward in the clinical armitarium. The RELEVANCE study has intriguing assumptions in place regarding the diverse practice of the modern practitioner in regards to R-chemo, but appropriately tackles practical inclusion criteria that have historic insight and the international flavor will almost guaranteeing full accrual. Lastly, several targeted agents have conquered the phase I/II test while others have been left on the chopping block. PI3K, BTK, mTOR and BCL-2 inhibitors appear to have potential, but the crucial next step will be appropriate pairings that compliments pre-clinical mechanisms and spares synergistic toxicities. A fate that will be almost certainly be tested with PI3K/mTOR dual inhibitors in the near future. Towards that goal, accrual into well designed clinical trials and incorporation of rationale correlative studies may usher in evidence for patient specific algorithms that may turn a relentless disease into a permissible memory.

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Table 1

Follicular Lymphoma International Prognostic Index (FLIPI) and FLIPI2

iNHL Prognostic Factors	
FLIPI	**FLIPI2**
Age >60	Age > 60
Ann-Arbor stage >2	Elevated LDH
Elevated LDH	Nodal site > 6 cm
Hgb < 12	Beta-2 microglobulin
Number nodal sites > 4	Bone marrow involvement

Table 2

NLBI and GELF treatment criteria

iNHL Treatment Criteria	
BLNI Criteria (Any one)	**GELF Criteria (Any one)**
Rapid disease progression	Lesion > 7 cm
End organ damage	3 nodal sites > 3 cm
Renal infiltration	Substantial splenomegaly
Bone lesions	Compression (ureteral, epidural)
Cytopenias	Serous effusions
	Cytopenias

Table 3

Selected planned/ongoing clinical trials in iNHL

First-line therapy
NCT00770224 Iodine I 131 Tositumomab, Rituximab, and Combination Chemotherapy in Treating Patients With Previously UntreatedStage II, Stage III, or Stage IV Follicular Non-Hodgkin Lymphoma. (SWOG)
NCT01234766 Bendamustine and Rituximab Followed by 90-yttrium (Y) Ibritumomab Tiuxetan for Untreated Follicular Lymphoma. (Fol-BRITe)
NCT01216683 Bendamustine Hydrochloride and Rituximab With or Without Bortezomib Followed by Rituximab With or Without Lenalidomide in Treating Patients With High-Risk Stage II, Stage III, or Stage IV Follicular Lymphoma.
NCT01476787 Combined Rituximab and Lenalidomide Treatment for Untreated Patients With Follicular Lymphoma. (RELEVANCE)
NCT00720876 Vorinostat and Rituximab in Treating Patients With Indolent Non-Hodgkin Lymphoma
Relapsed disease
NCT01429025 Rituximab, Bendamustine Hydrochloride, and Lenalidomide in Treating Patients With Refractory or Relapsed Indolent Non-Hodgkin Lymphoma.
NCT01479842Rituxan/Bendamustine/PCI-32765 in Relapsed DLBCL, MCL, or Indolent Non-Hodgkin's Lymphoma.
NCT01282424 Efficacy and Safety Study of CAL-101 in Patients With Indolent B-Cell Non-Hodgkin Lymphoma. (DELTA)
NCT00671112 Everolimus and Bortezomib in Treating Patients With Relapsed or Refractory Lymphoma.
NCT00406809 A Study of ABT-263 in Subjects With Relapsed or Refractory Lymphoid Malignancies.
Transplantation
NCT00807196 Zevalin With Non Myeloablative Allogeneic Stem Cell Transplantation in Patients With Non Hodgkin Lymphoma.