Treatment of Relapsed/Refractory Hodgkin Lymphoma

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Contents

4.1 Introduction

In the past 10–20 years, the treatment outcome for patients with pediatric Hodgkin disease (HL) has improved remarkably; however, 10–20% of the patients still relapse. Historically, retrieval approaches for patients with recurrent HL have utilized regimens that were previously used in frontline therapy. Generally, the degree of response to these regimens predicted the ability to rescue patients. In children and adolescents, the tolerance of salvage therapy has been exceptional, permitting the evaluation of novel therapeutic strategies. Given this fact, the introduction of new chemotherapeutic, immunologic and biologic agents is necessary to improve the response rate of pediatric patients with recurrent/refractory HL. Because of the significant risk of treatment-related secondary malignancies in pediatric patients associated with the use of alkylating agents and epipodophyllotoxin chemotherapy, agents frequently used in the treatment of HL (Krishnan et al. 2000; Pedersen-Bjergaard et al. 1997; Wheeler et al. 2001), alternative therapeutic approaches for retrieval that are both efficacious and safe must be considered for pediatric patients with relapsed/refractory HL.

4.2 Strategies for Re-induction

Combined modality chemotherapy and radiotherapy have resulted in the cure of 80–90% of pediatric patients with HL. Approximately 10–20% of patients with advanced stage HL relapse after front-line treatment. Historically, a failure to respond to treatment with standard-dose conventional chemotherapy has resulted in low complete remission rates and minimal

survival benefit. Longo et al. reported a median survival of 16 months in patients who never attained a CR in a series of 51 patients treated with Methotrexate, Oncovin, Procarbazine and Prednisone (MOPP) (Longo et al. 1992). Likewise, Bonfante et al. reported similar results in patients who failed MOPP or MOPP/ABV hybrid or alternating regimens with a long-term event-free survival (EFS) of 8% (Bonfante et al. 1997). Failure to respond or relapse is directly related to the duration of the initial response (Longo et al. 1992). Progression during induction therapy or within 12 months of completion of treatment resulted in a dismal prognosis with 5-year disease-free survival rates of 0% and 20%, respectively (Longo et al. 1992). Relapses occurring 12 months or later were amenable to salvage chemotherapy, but overall survival rates were 20–50% with conventional chemotherapy (Fisher et al. 1979; Longo et al. 1992; Viviani et al. 1990).

4.2.1 Role of Re-induction Chemotherapy

Response to cytoreductive (re-induction) chemotherapy prior to high-dose therapy in patients with relapsed/refractory HL predicts overall survival (OS) regardless of the type of salvage therapy. Yuen et al. reported that sensitivity of disease reflected by response to cytoreductive therapy prior to high-dose therapy in patients with relapsed/refractory HL was a significant predictor of OS regardless of the type of salvage therapy (Yuen et al. 1997). Likewise, Rapoport et al. demonstrated that high-dose therapy was most effective for low-risk patients who enter with minimal or sensitive disease (Rapoport et al. 1993). In this series, minimal disease status at the time of transplant was the major predictor of improved EFS for patients with HL and non-Hodgkin's lymphoma (NHL). Moskowitz et al. reported on 65 relapsed/refractory HD patients treated at Memorial Sloan-Kettering Cancer Center who underwent induction chemotherapy with ICE prior to high-dose therapy; there was a response rate to ICE of 88% and an EFS of 68% for patients (median follow-up 43 months) who underwent transplantation (Moskowitz et al. 2001). Ā e EFS among HL patients with a positive response to salvage was 58% vs 35% in those who did not respond (p=0.12). Ā us, the advantages of induction chemotherapy may be to decrease tumor burden before high-dose therapy and to select appropriate candidates for high-dose treatment. Further well-designed prospective studies are needed to test and substantiate this hypothesis.

4.2.2 Standard Re-induction with ICE

As single agents or in combination, the chemotherapeutic agents ifosfamide, carboplatin, and etoposide have been effective in the treatment of adult (Moskowitz et al. 1999, 2001) and pediatric patients with HL and NHL. Consequently, the combination is a commonly used re-induction regimen in patients with relapsed/refractory disease. Kung et al. reported a response rate of 80% in a phase II trial in pediatric patients with recurrent non-Hodgkin lymphoma treated with ICE (Kung et al. 1995). Limited data, however, are available from pediatric phase I/II studies regarding response in HL to ICE. In the one available study, Moskowitz et al. at Memorial Sloan-Kettering Cancer Center reported an 88% response rate with ICE in a combined trial with adult and pediatric patients with relapsed/refractory HL (Moskowitz et al. 2001).

Observation of an increased incidence of treatment-related secondary malignancies associated with the use of alkylating agents and the epipodophyllotoxins (etoposide and teniposide) mandates consideration of alternative therapeutic approaches for re-induction that incorporate novel, effective, and less toxic agents. Etoposide, which has been shown to be a highly active agent in the treatment of HL and other pediatric tumors, has been associated with the development of myelodysplastic syndrome and secondary acute myelogenous leukemia. Given this finding, alternative re-induction approaches must be explored utilizing combinations of agents with non-overlapping mechanisms of action and toxicity as well as acceptable short- and long-term safety profiles. Two re-induction regimens incorporating novel agents with acceptable toxicity profiles are being evaluated in Children's Oncology Group (COG) phase II trials combining the chemotherapeutic agents, ifosfamide and vinorelbine (AHOD00P1) and gemcitabine and vinorelbine (AHOD0321).

4.2.3 Re-induction Therapy with Ifosfamide/ Vinorelbine (IV)

Vinorelbine (Navelbine, VRB), a semisynthetic alkaloid, exhibits marked clinical activity in HL and NHL (Borchmann et al. 1998; Devizzi et al. 1994, 1996). Similar to other vinca alkaloids, the mechanism of action of VRB is inhibition of microtubule formation (Toh et al. 1998). Vinorelbine, however, demonstrates more selective inhibition of mitotic microtubule formation as opposed to the inhibition of neural axonal formation observed with vinca alkaloids, thereby diminishing the likelihood of neurotoxicity. Preclinical studies indicated broad-spectrum antitumor activity in in vitro and in vivo model systems in a variety of murine cell lines, L1210 leukemia, P388 leukemia, B16 melanoma, and human tumor cell lines (leukemia, colorectal carcinoma, central nervous system, breast carcinoma, non-small-cell and small-cell lung carcinoma) (Toh et al. 1998).

Vinorelbine has been studied in adult and pediatric phase I clinical trials. The adult maximum tolerated dose (MTD) ranged from 30 to 35 mg/m^2/week. Adult phase I studies evaluated the toxicity profile of VRB administered on a weekly intravenous bolus dose schedule. Extensive experience in these studies has demonstrated that VRB has limited severe toxicities. The dose-limiting toxicity (DLT) was granulocytopenia, noted in 60% of patients. The predominant nonhematologic toxicities include transient elevation in hepatic transaminases, alkaline phosphatase, and bilirubin. Reversible peripheral neuropathy was observed in 20% of patients. Asthenia, injection site reactions (phlebitis < 5%) nausea, vomiting, and constipation were uncommon. In the phase II studies, response rates as high as 50% have been reported when VRB is given weekly as a single agent to heavily pretreated patients with relapsed or refractory HL (Rule et al. 1998; Devizzi et al. 1996), with some complete responses (CR) seen. Grade 3–4 granulocytopenia was reported in ~ 50% of patients. Local injection site reactions and constipation were uncommon. In a pediatric phase I clinical trial in patients with recurrent or refractory pediatric malignancies, the MTD was established at 33.75 mg/m^2/dose. In a phase II study conducted by the Children's Cancer Group, A09705, VRB was administered on a weekly schedule for 6 weeks in 50 children with recurrent or refractory pediatric malignancies. Due to significant neutropenia resulting in frequent treatment delays, the dose of VRB was reduced from 33.75 mg/m^2/dose to 30 mg/m^2/dose. Nonhematologic toxicity at either dose seemed to be less frequent than that reported in adult trials.

The combination of ifosfamide and vinorelbine (IV) has been evaluated in a phase II trial in adult patients with refractory/recurrent HL (Bonfante et al. 1997). An overall response rate of 80% (40% CR and 40% PR) was achieved with a median of two cycles of IV in 20 patients (Bonfante et al. 1997). The results were particularly encouraging in patients with extranodal disease who had a response rate of 89%. This combination was well-tolerated with no apparent cumulative toxicity after as many as ten consecutive cycles. The toxicity profile of this combination was limited to grade 3–4 neutropenia in only 50% of the cycles with a median duration of 4 days. Fanconi's tubular dysfunction was not observed after IV as with ICE (Ho 1995). In the pediatric setting, a phase II COG pilot study (AHOD00P1) was conducted to evaluate IV as a novel re-induction regimen for patients with relapsed/refractory HL prior to stem cell transplantation (Trippett et al. 2004). The schedule of administration comprised a 21-day treatment cycle consisting of ifosfamide 3000 mg/m^2/day administered by continuous intravenous infusion for 4 consecutive days and VRB 25 mg/m^2/dose administered by intravenous bolus on days 1 and 5. The treatment schema is shown in Fig. 4.1. The primary objectives of this study were to assess the toxicity, capability to mobilize hematologic stem cells, and response rate of this novel re-induction regimen. An acceptable toxicity profile was demonstrated with the predominant toxicity being reversible myelosuppression. The major grade 3 toxicities included neutropenia (81%), thrombocytopenia 44%, and anemia 69%. The incidence of nephrotoxicity and neurotoxicity was negligible, 3% and < 1%, respectively. Acceptable stem cell mobilization rates were noted as well. Response data in pediatric patients with heavily pretreated relapsed/refractory HL demonstrated an objective response rate (ORR; complete/partial response: CR/PR) of 78%. Successful mobilization of peripheral blood stem cells was accomplished in the majority of patients

(Trippett et al. 2004). Ā ese data substantiate IV as an acceptable re-induction regimen for pediatric patients with relapsed/refractory HL.

4.3 High-Dose Therapy

Since its introduction 20 years ago, high-dose therapy with autologous stem cell rescue has become the treatment of choice for patients with relapsed or refractory HL. Ā e increase in the use of high-dose therapy is due largely to the marked reduction in early transplant-related mortality, improved disease free-survival, and widespread availability of this approach. In multiple series, sustained remissions have been seen after high-dose therapy and autologous bone marrow rescue, and more recently, peripheral stem cell transplantation with response rates reaching 50% in most studies and early transplant-related mortality rates <10%. A variety of high-dose therapy regimens including cyclophosphamide, busulfan, etoposide (CBV), busulfan, etoposide, cytarabine, melphalan (BEAM), or high-dose melphalan with or without total body irradiation (TBI) have been used; however, none of these regimens have been shown to be superior (Chopra et al. 1993; Jagannath et al. 1989; Kessinger et al. 1991; Reece et al. 1994; Schmitz et al. 2002). Despite maximal intensification of therapy with autologous stem cell rescue, only 40–50% of patients are salvaged. Ā e predominant reason for failure in patients undergoing salvage therapy is relapse. Ā erefore, the need for effective novel retrieval strategies as an adjunct to high-dose therapy is paramount.

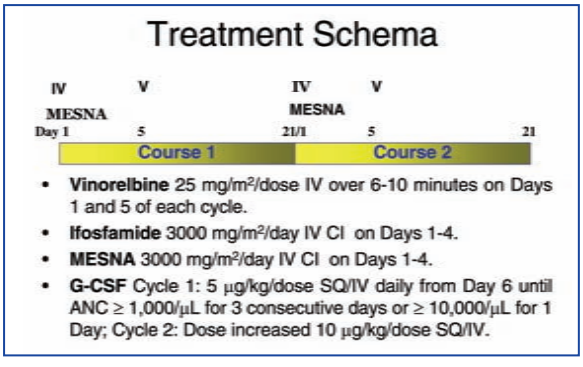

Figure 4.1

Treatment schema for AHOD00P1, Phase II Study of Ifosfamide/Vinorelbine

In adult patients, high-dose therapy with autologous hematopoietic stem cell rescue (ASCR) has become the standard option for salvage therapy over conventional allogeneic stem cell transplantation in patients with relapsed or refractory HL, with reported survival rates ranging between 30 and 50%. Ā e role of conventional allogeneic stem cell transplantation has been limited to younger patients because of high non-relapse mortality rates (43–61%) and graft-versus-host disease (GVHD) (Akpek et al. 2001; Anderson et al. 1993; Milipied et al. 1996; Gajewski et al. 1996). Retrospective data in children undergoing ASCT, although limited, have demonstrated similar 5-year OS, EFS, and PFS rates to that of adult patients, with a survival advantage for patients with refractory disease or relapse within 12 months of completion of front-line therapy (Baker et al. 1999; Lieskovsky et al. 2004). Ā e therapeutic benefit of high-dose therapy in patients who relapse more than 1 year after completion of front-line therapy remains controversial. In this regard, Ardeshna et al. reported a survival advantage in this group of patients over salvage with conventional chemotherapy (Ardeshna et al. 2005). Conversely, the United Kingdom Children's Cancer Study Group concluded that overall survival in patients treated with ASCT did not differ significantly from that of those treated with conventional salvage therapy following a retrospective study in 51 pediatric patients with relapsed or refractory HL (hazard ratio = 1.5; 95% confidence interval= 0.9–8.2; p= 0.4) (Schmitz et al. 2002). Moreover, survival data did not differ among the patients who underwent ASCT or conventional chemotherapy if the duration of first remission was less than or greater than 1 year (p = 0.5; stratified log-rank). Despite these conflicting results, the general consensus is that ASCT enhances the potential for long-term cures and should be considered in children and adolescents with relapsed/refractory HL.

Although high-dose therapy appears to be an effective therapeutic modality for the treatment of recurrent or refractory HL, approximately 40–50% of children and adolescents will experience a subsequent relapse of their disease. Ā e patterns of relapse follow-

ing high-dose chemotherapy occur in the majority of the cases (81%) in the sites of prior disease. However, first-time presentation of intrapulmonary disease has been demonstrated in 53% of the cases (Stoneham et al. 2004). Several prognostic factors have been identified in the adult literature that determine the outcome after transplantation including bulk of disease at transplantation, systemic symptoms at relapse, extranodal disease at relapse, number of prior treatment regimens, duration of initial remission, performance status, and relapse within a prior radiation field (Bonfante et al. 1997; Burns et al. 1995; Chopra et al. 1993; Crump et al. 1993; Jagannath et al. 1989; Moskowitz et al. 2001; Rapoport et al. 1993). In the pediatric literature, additional prognostic factors include female sex, interval from diagnosis to ASCT <15 months, elevation of LDH levels, and disease sensitivity at the time of ASCT (Baker et al. 1999; Lieskovsky et al. 2004). Ā e most significant factors in children that are predictive for poor OS, EFS, and PFS after ASCT as in adults were extranodal disease at the time of relapse and bulky mediastinal mass at the time of transplantation. Based upon these findings, additional therapeutic approaches must be explored to augment the response to high-dose chemotherapy.

4.3.1 Immunomodulation as a Therapeutic Strategy to Augment High-Dose Therapy

Ā e observation that immunologic effector mechanisms are not cross-resistant with chemotherapy and radiation therapy suggests a potentially beneficial role of immunotherapy (Fuchs et al. 1995; Kontny et al. 1998). Further support includes data demonstrating an allogeneic effect after bone marrow transplantation in HL, albeit offset by transplant-related morbidity (Anderson et al. 1993; Jones et al. 1991). Infusion of donor lymphocytes has been reported to produce a response in recurrent HL after bone marrow transplantation (Russell et al. 1996). Immunomodulation with interferon-γ and interleukin-2 (IL-2) following autologous stem cell rescue has also been demonstrated to reduce the rate of relapse and to improve survival compared to historical controls (Nagler et al. 1997). Based on these data, investigators in the COG are conducting a phase II clinical trial, ADHOD0121, evaluating the feasibility and efficacy of a novel therapeutic approach that combines high-dose therapy with immunotherapy with cyclosporine, interferon-γ, and IL-2 to stimulate autologous GVHD during recovery following ASCR which may result in an antitumor effect (Chen et al. 2005). Ā e primary aims of the study are to improve survival in patients with recurrent or refractory HL and to provide proof of principle for immunotherapy after autologous stem cell rescue (ASCR). Ā e initial or feasibility phase of the study has been completed. Patients with biopsy-proven recurrent or refractory HL were enrolled in the study and received immunomodulation with cyclosporine, interferon-γ, and IL-2 following high-dose BEAM as a preparative regimen and ASCR. Expected reversible complications including febrile neutropenia, pancytopenia, nausea, vomiting, anorexia, mucositis, and electrolyte disturbances were observed. Two patients developed pneumonitis after receiving immunotherapy, one of whom died of respiratory failure 6 weeks after study entry. Ā e latter patient received only 2 doses of IL-2 before developing pneumonia. Bronchoalveolar lavage failed to demonstrate an etiology for the pneumonia; however, a culture obtained from an open lung biopsy was positive for *Staphylococcus epidermidis*. One patient developed a rash, and one patient developed liver abnormalities during immunotherapy. Peripheral blood samples were obtained at weekly intervals during immunotherapy to test for autoreactivity in mixed lymphocyte cultures and by cytokine assays with autologous stimulator cells. In 11 of 14 evaluable patients, there was significant in vitro lymphocyte autoreactivity. Based upon these findings, the immunotherapy regimen was found to have acceptable tolerance and induced autoreactivity in a sufficient proportion of patients to warrant proceeding with the second phase of the study, testing the efficacy of the regimen by randomization of patients with chemosensitive recurrent/refractory HL to receive immunotherapy or not following conditioning with BEAM and ASCR. Patients with refractory HL will undergo nonrandom assignment to receive immunotherapy.

4.3.2 Reduced-Intensity/Non-myeloablative Allogeneic Stem Cell Transplantation

Ā e role of reduced-intensity allogenic or non-myeloablative stem cell transplantation (NST) as a salvage approach in HL remains controversial. Ā e incorporation of reduced-intensity conditioning utilizing fludarabine-containing regimens with or without early cyclosporine withdrawal and donor lymphocyte infusions provides potential advantages including sufficient immunosuppression for allogeneic engraftment, decreased toxicity in comparison to standard high-dose conditioning regimens, reduction in nonrelapse-related mortality rates, as well as the potential induction of a graft-versus-lymphoma (GVL) effect to improve efficacy. Recent reports of favorable outcomes with NST in small cohorts of patients with recurrent/refractory HL have resulted in renewed interest in allografting in HL (Carella et al. 2001; Peggs et al. 2005; Phillips et al. 1989). Peggs et al. reported a response rate of 56% (8 CR, 1 PR) in a series of 49 patients with multiply relapsed HL who had progression of disease after prior autologous transplantation with a nonrelapse-related mortality rate of 16.3% at 730 days (7.3% for patients with related donors and 34.1% for those with unrelated donors). Despite these intriguing results, the efficacy of transplantation after reduced-intensity conditioning remains controversial. In several multicenter studies, 2-year progression-free survival rates have been reported ranging from 16 to 26%. A major factor in determining outcome related to NST was disease status prior to transplantation (Robinson et al. 2004). Ā e disease status prior to NST was the only predictive factor for a high relapse rate. Chemo resistant patients demonstrated a significantly worse PFS rate.

Currently, NST has been utilized in patients with refractory HL as an adjunct to high-dose therapy with ASCR or as an alternative salvage approach in patients with multiply relapsed HL after failure of ASCT. To date, NST has been restricted to use in high-risk patients with chemosensitive disease, decreased tumor burden prior to allografting, and as a treatment of choice in patients where the toxicity of standard ablative therapy is considered unacceptable, i.e., patients with organ dysfunction or comorbidities. Patients with unresponsive or bulky residual disease have been considered poor candidates for treatment with this modality.

Confounding variables which restrict the ability to assess the impact of NST include the small numbers of patients treated, patient selection, and the inability to confirm a GVL effect in patients undergoing this procedure. Ā e value of NST will ultimately require validation of the efficacy of this modality in randomized clinical trials. Future considerations to improve the outcome after NST include optimization of preparatory regimens and the development of techniques to selectively eliminate alloreactive T cells responsible for GVHD from T cells associated with GVL and infection control potential.

4.4 Salvage Strategies Following Transplantation

Historically, salvage approaches for patients who fail second-line therapy have consisted of either sequential single-agent chemotherapy or multiagent chemotherapy. In patients who receive further treatment after failure of high-dose therapy and demonstrate continued chemosensitivity, a survival advantage has been reported (13 vs 4 months median, $p = 0.0001$) (Schmitz et al. 2002). A trend toward longer survival was observed in patients whose disease recurred later than 6 months following high-dose chemotherapy particularly in those who received combination chemotherapy. Ā us, administration of additional therapy in patients who experience treatment failure following high-dose therapy should be considered. Further understanding of the biology of HL may broaden the spectrum of options of therapeutic strategies by the development of targeted therapy.

Ā e introduction of novel therapeutic approaches incorporating new single agents or combination chemotherapeutic regimens and/or targeted biologic or immunologic agents is needed to overcome resistance, to provide a potential benefit to patients who fail treatment with first- and second-line therapy, and to minimize the short- and long-term toxicity in heavily pretreated patients. Ā e following sections provide a summary of the variety of novel therapeutic approaches that are currently being investigated.

4.4.1 Combination Chemotherapy with Gemcitabine/Vinorelbine (GEM/VRB)

Gemcitabine, 2',2'–difluorodeoxycytosine (GEM), a deoxycytidine analog which inhibits DNA synthesis and repair (Plunkett et al. 1995), has demonstrated significant single-agent activity in patients with relapsed or refractory HD. Like cytosine arabinoside, GEM is a prodrug which requires intracellular phosphorylation by deoxycytidine kinase to the active diphosphate and triphosphate forms. In vitro, GEM has a higher affinity for deoxycytidine kinase than cytarabine, as well as a longer intracellular retention (Heinemann et al. 1988). In adults, the maximally tolerated dose (MTD) of GEM varied significantly depending on both the schedule of administration (frequency and duration of infusion) and patient factors (e. g., prior chemotherapy). Adult MTDs ranged from 800 mg/m^2 in heavily pretreated patients to 4800 mg/m^2 when given as a prolonged infusion over 480 min to less heavily pretreated patients (Grunewald et al. 1992). The MTD in the pediatric phase I in children with refractory hematologic malignancies (leukemia/NHL) was 3600 mg/m^2/week (10 mg/m^2/min for 360 min) when administered weekly for three consecutive weeks (Steinherz et al. 2002). The DLT was hepatotoxicity. Some 30–50% of patients exhibited allergic-type symptoms including fever, rash, or myalgia. In phase II trials of GEM as a single agent in the treatment of patients with relapsed or refractory lymphomas, a range of dosing and schedules has been used (Bernell and Ohm 1998; Dumontet et al. 2001; Fossa et al. 1999; Lucas et al. 1999; Santoro et al. 2000; Savage et al. 2000; Venkatesh et al. 2004; Zinzani et al. 2000). Overall response rates in HL have been as high as 39%–43% (Santoro et al. 2000; Zinzani et al. 2000).

As a single agent, GEM has a favorable safety profile with a similar spectrum of toxicities in adults and children (Green 1996). The major toxicity was myelosuppression. Sporadic grade 4 lymphopenia, grade 3 transaminase elevation, abnormal clotting studies, myalgias, fainting, grade 3 proteinuria, grade 3 constipation, and hypotension with fever were also reported. The incidence of noncardiogenic pulmonary edema (NCPE) in adults was low (<2%). NCPE is a potentially fatal complication of therapy with GEM characterized by the simultaneous presence of grade 3 or 4 hypoxia and bilateral alveolar infiltrates noted on chest radiograph persisting for at least 3 days without evidence of other etiologies, i.e., congestive heart failure, infection, left atrial hypertension, metabolic abnormalities, or cancer-related causes (e. g., malignant pericarditis). No cases of NCPE were reported in children in 115 administered courses of gemcitabine (Reid et al. 2004).

VRB as previously described has significant single-agent activity (50%) in adult and pediatric patients with relapsed or refractory HL with a limited toxicity profile. Preclinical models have demonstrated additive activity when GEM is combined with VRB with little increased toxicity over a wide range of doses (Herbst et al. 2001). Published data regarding the use of this combination in adult patients with relapsed/refractory HL has demonstrated significant antitumor activity particularly in patients with a second recurrence after high-dose therapy. In one series, six of eight treated patients with HL had disease stabilization or response following treatment with GEM 1000 mg/m^2 and VRB 25 mg/m^2 on days 1 and 8, followed by G-CSF support until neutrophil recovery (Spencer et al. 2002). In the Memorial Sloan-Kettering Cancer Center experience, a larger series of 13 adult patients with relapsed or refractory HL following autologous stem cell transplantation received GEM 1275 mg/m^2 and VRB 30 mg/m^2 on a biweekly schedule (Hamlin et al. 2002). Of 178 treatments administered, 172 were given at the intended dose level. The ORR was 62% (6 PRs and 2 CRs). The median time to maximum response was six cycles (range 5–26). In contrast to the high rates of pulmonary toxicity observed following front-line pilot studies incorporating bleomycin with GEM, neither series reported NCPE (Bredenfeld et al. 2004; Friedberg et al. 2003).

Anecdotal cases have been reported in the literature using the GEM/VRB combination as a salvage regimen after ASCT in the pediatric setting (Ozkaynak and Jayabose 2004). A COG phase II study, AHOD0321, is currently underway in an effort to introduce novel and hopefully nontoxic agents to the therapeutic approach for patients with relapsed/refractory HL. This study will evaluate the efficacy and toxicity of the combination gemcitabine/vinorelbine in a large series of

pediatric patients in second or greater relapse or refractory HL. The schedule of administration will comprise a 21-day treatment cycle consisting of two weekly doses of gemcitabine administered at 1000 mg/m^2/dose and vinorelbine 25 mg/m^2/dose. The schema of the therapeutic regimen is shown in Fig. 4.2. It is hoped that the combination GEM/VRB may show promise as a novel salvage approach for children and adolescents with relapsed or refractory HL.

4.4.2 Molecular Targeting of the NF-κB Pathway

Better understanding of the mechanism of malignant transformation of HL and the role of nuclear factor-kappa B (NF-κB) in this process affords the opportunity to develop biologically based therapy for HL (Krappmann et al. 1999; Stein and Hummel 1999). Recent studies have evaluated the origin of the Hodgkin and Reed Sternberg (H/RS) cells (Kornacker et al. 1999). Studies of single-cell DNA amplification have also documented the importance of signaling through NF-κB transcription factor both in the proliferation of H/RS cells and in the suppression of apoptosis (Bargou et al. 1996; Krappmann et al. 1999). More importantly, inhibition of this pathway also inhibits cell proliferation, induces apoptosis, and renders H/RS cells less able to form tumors when transplanted into nude mice (Bargou et al. 1997).

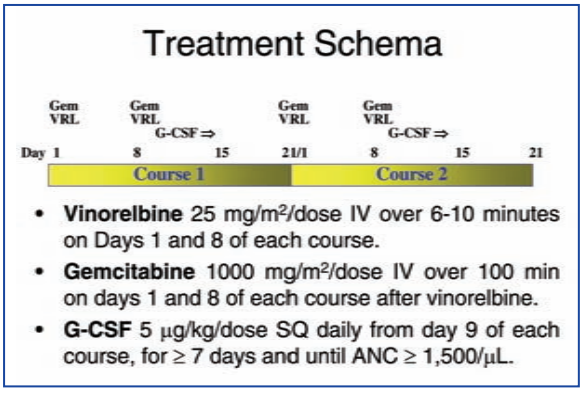

Figure 4.2
Treatment schema for AHOD321, Phase II Study of Gemcitabine/Vinorelbine

4.4.2.1 Activation of NF-κB

NF-κB, a nuclear transcription factor, is constitutively activated in HL. Extensive research has demonstrated that NF-κB regulates the expression of a variety of genes that play a crucial role in viral replication, tumorigenesis, apoptosis, various autoimmune diseases, and inflammation (Younes et al. 2003). NF-κB under normal conditions is found in the cytoplasm in an inactive state as a heterotrimer consisting of p50, p65, and IκBα subunits (Younes et al. 2003). In nonproliferative cells, the inhibitor protein IκB sequesters NF-κB in the cytoplasm. Cellular stress results in ubiquitination and the subsequent degradation of IκBα. When IκBα is degraded, nuclear localization signals are exposed on the p50-p65 heterodimer, resulting in nuclear translocation of free NF-κB, phosphorylation, and binding to a specific DNA sequence that results in DNA transcription (Younes et al. 2003) (Figs. 4.3–4.5). Subsequently, the promoter regions of numerous genes are activated, including genes encoding for several antiapoptotic proteins such as bcl-2, X-linked inhibitor of apoptosis protein (XIAP), and c-Jun N-terminal kinase (JNK) (Karin et al. 2002; Li and Stark 2002).

Constitutive activation of NF-κB in HD can occur through a variety of mechanisms, including NF-κB gene amplification, NF-κB chromosomal rearrangements, IκB mutations, induction of IκB kinases (IKK), and the induction of upstream regulators of NF-κB (Younes et al. 2003). Mechanisms of NF-κB activation found in H/RS cells include amplification of IκB kinase activity (Krappmann et al. 1999), C-terminal IκB mutations (Emmerich et al. 1999), EBV-mediated LMP-1 expression (McFarland et al. 1999), CD30 overexpression (Horie et al. 2002), c-Jun overexpression (Matthas et al. 2002), and increased expression of soluble RANKL (Fiumara et al. 2001). Because NF-κB activation can enhance the expression of several proteins implicated in protection from apoptosis in H/RS cells (Hinz et al. 2002), NF-κB inhibition is postulated to sensitize malignant cells to chemotherapy and radiation (Turco et al. 2004; Jeremias et al. 1998; Wang et al. 1999). Several in vitro studies support this hypothesis. Pajonk et al. demonstrated that NF-κB inhibition enhanced H/RS cell sensitivity to both radiotherapy and chemotherapeutic agents (Pajonk et al. 2000).

Ā us, inhibition of NF-κB would be an attractive biologic or molecular targeted strategy in the treatment of relapsed/refractory HL.

4.4.2.2 Inhibition of NF-κB Through Proteasome Inhibition

Ā e focus of future targeted studies in pediatric patients with HL will incorporate novel agents (chemotherapeutic and biologic agents) and therapeutic strategies which act to perturb the NF-κB pathway through inhibition of NF-κB. One strategy to inhibit NF-κB would be through proteasome inhibition which results in the stabilization of IκBα. Current novel therapeutic strategies incorporating proteasome inhibition are underway in a variety of cancers.

Bortezomib (Velcade, PS341), a dipeptidyl boronic acid, is a selective inhibitor of NF-κB activation and of the ubiquitin proteasome pathway (UPP), which is essential for the degradation of most short-lived and many long-lived intracellular proteins in eukaryotic cells (Adams et al. 1999) (Fig. 4.6). Important regula-

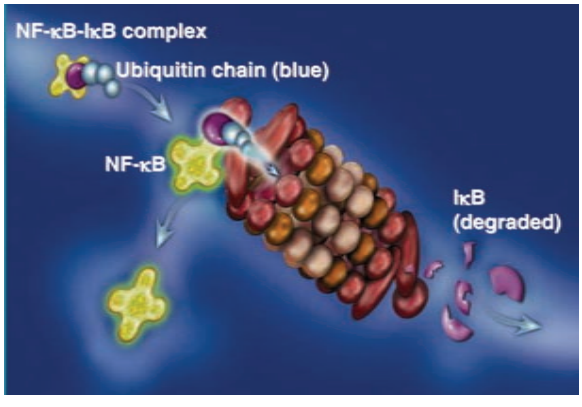

Figure 4.3

Sequential activation of NF-κB after IκB degradation by the proteasome (courtesy of Millenium Pharmaceuticals, Inc.)

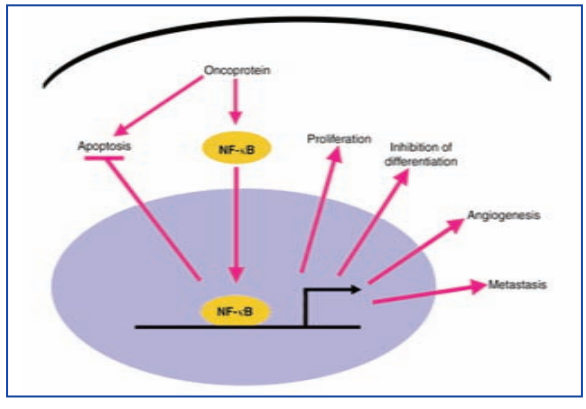

Figure 4.5

Transcriptional activation of NF-κB (courtesy of Millenium Pharmaceuticals, Inc.)

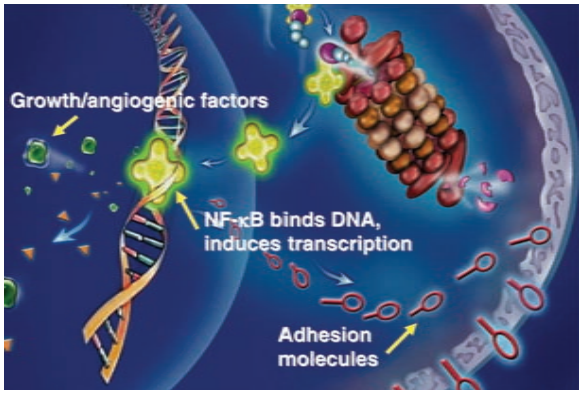

Figure 4.4

Effects of NF-κB activation (courtesy of Millenium Pharmaceuticals, Inc.)

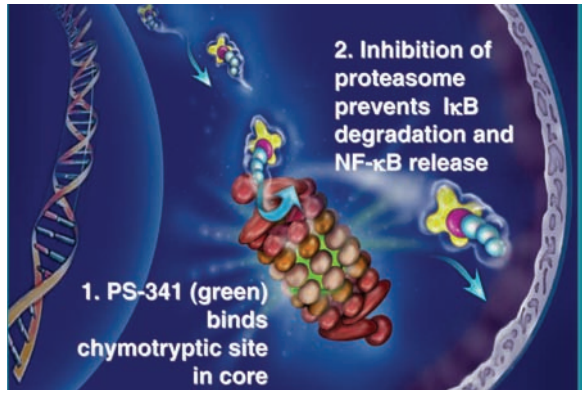

Figure 4.6

Proteasome inhibition by Bortezomib (PS341) (Courtesy of Millenium Pharmaceuticals, Inc.)

tory proteins affected by inhibition of the UPP system include NF-κB, p53, bcl-2, and other cell cycle regulatory proteins such as the cyclin-dependent kinase inhibitors p21 and p27 (Hochstrasser 1995). Proteasome inhibition stabilizes many cell cycle regulatory proteins and appears to sensitize malignant cells to apoptosis. Proteasome inhibition can also change the balance of pro- and anti-apoptotic proteins in the mitochondrial membrane and may block anti-apoptotic responses to chemotherapy (Adams et al. 2000).

Bortezomib specifically inhibits the 26S proteasome, an ATP-dependent multi-subunit protein that degrades proteins involved in multiple cellular processes, including cell cycle regulation, transcription factor activation, apoptosis, and cell trafficking (Tiecher et al. 1999). Bortezomib has been shown in vitro to be cytotoxic in leukemia and cancer cell lines due to induction of apoptosis (Zheng et al. 2004; Schenkein 2002). Cell death is believed to be preceded by p21WAF1/CIP1 accumulation (an alternative marker of proteasome inhibition) and by cleavage of PARP and Rb proteins and nuclear fragmentation. Apoptosis following proteasome inhibition is seen in malignant HL cell lines (Zheng et al. 2004; Schenkein 2002) as well as in primary HL cells (Pajonk et al. 2000), but not in normal hematopoietic progenitors (Masdehors et al. 2000). Although much preclinical work has focused on the inhibition of NF-κB following proteasome inhibition, the precise mechanism of bortezomib cytotoxicity is not clear. 26S-proteasome inhibition results in rapid cytochrome c release (3–6 h) from the mitochondrial membrane, followed by activation of caspases 8 and 9 (12 h) and caspases 3 and 7 (24 h) (Marhansky et al. 2001; Ling et al. 2002). Bortezomib enhanced in vitro H/RS sensitivity to gemcitabine (Schenkein 2002, 2005), TNF-related apoptosis-inducing ligand (TRAIL) (Zheng et al. 2004) and dexamethasone (An et al. 2004). Bortezomib has also enhanced solid tumor sensitivity to a variety of chemotherapy agents, including cyclophosphamide, in xenograft models (Teicher et al. 1999). Recent data demonstrated that the action of bortezomib in Hodgkin-derived cell lines may be enhanced in vitro and in vivo when preceded by anti-CD30 antibody activation of NF-κB (Boll et al. 2005). Boll et al. demonstrated that CD30 stimulation via 5F11, a fully humanized monoclonal antibody directed against CD30, activates NF-κB and its target cellular Fas-associating protein with death domain-like interleukin-1B-converting enzyme (FLICE) inhibitory protein (c-flip), which can also be inhibited by bortezomib. Cytotoxic synergy in vitro and in vivo was seen with the combination of 5F11 and bortezomib.

4.4.2.3 Adult Clinical Trials

Bortezomib has been evaluated as a single agent in multiple myeloma and NHL in adults. The MTD in adults varied with dosing schedule and ranged from 1.04 mg/m^2 (twice weekly for 4 weeks every 6 weeks) to 1.6 mg/m^2 (weekly for 2 weeks every 3 weeks) (Orlowski et al. 2002; Richardson et al. 2004). The most frequently reported adverse events (≥ 10%) among the 123 patients with advanced malignancies treated in phase 1 studies with bortezomib included fatigue (58%), anemia (47%), nausea (45%), constipation (43%), diarrhea (41%), vomiting (33%), headache (26%), pyrexia (24%), dyspnea (22%), abdominal pain (20%), and thrombocytopenia (19%). Grade 3 or grade 4 AE reported included thrombocytopenia (9%), anemia (6%), diarrhea (9%), and fatigue (4%) (Orlowski et al. 2002; Papandreou et al. 2004).

Two published studies have examined the efficacy of bortezomib as a single agent in phase II trials in adults with relapsed/refractory NHL (O'Connor et al. 2005; Goy et al. 2005). O'Connor et al. conducted a phase II clinical trial in indolent NHL and mantle cell lymphomas (O'Connor et al. 2005). The ORR (3 CR, 8 PR) was 50% in 24 evaluable patients. The toxicity profile was acceptable, consisting of one episode of grade 4 hyponatremia and grade 3 lymphopenia (58%) and thrombocytopenia (41%). Goy et al. reported an ORR for patients with mantle cell lymphoma of 41% (6 CR, 6 PR) with a median follow-up time of 9.3 months (range 1.7–24 months) and an ORR of 19% (2 CR, 2 PR) in patients with other B-cell lymphomas (small lymphocytic lymphoma, diffuse large B-cell lymphoma, and Waldenstrom's macrogloblinemia). The toxicity profile demonstrated grade 3 thrombocytopenia (47%), gastrointestinal disturbances (20%), fatigue (13%), neutropenia (10%), and peripheral neuropathy (5%). Grade 4 toxicity occurred in 9 patients (15%),

and 3 deaths were reported from disease progression within 3 days of withdrawal from the study. Two additional studies are in progress to evaluate bortezomib as a single agent in HL and in combination with a conventional chemotherapeutic regimen with etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (EPOCH).

4.4.2.4 Pediatric Clinical Trials

A phase I study evaluating bortezomib in pediatric patients with relapsed/refractory solid tumors has been conducted (Blaney et al. 2004). The dosing schedule consisted of twice weekly bolus dosing of bortezomib administered for 2 consecutive weeks at either 1.2 mg/m^2 or 1.6 mg/m^2 followed by a 10-day rest period. Fifteen patients were enrolled in the study. Thrombocytopenia was the DLT in the 12 patients evaluable for toxicity. Grade 3 or 4 toxicities included neutropenia (3), anemia (2), thrombocytopenia (3), and transient elevation in ALT (1). Inhibition of 20S proteasome activity in children appeared to be dose-dependent, with an average inhibition 1 h after drug administration on day 1 of 67% + 7% at 1.2 mg/m^2 and 77% + 3% at 1.6 mg/m^2. A phase I study of bortezomib in relapsed/refractory pediatric leukemia is currently underway.

4.4.2.5 Novel Retrieval Strategies Incorporating Proteasome Inhibition with Bortezomib

By exploiting the potential targeted activity of bortezomib in relapsed/refractory HL through inhibition of NF-κB, a variety of therapeutic strategies is being explored. The German Hodgkin Study Group is currently evaluating a combination of bortezomib and dexamethasone in a relapsed setting. A phase II pilot study will be conducted by the COG, AHOD0521, evaluating the safety and efficacy of a novel re-induction regimen consisting of bortezomib in combination with the re-induction regimen IV. Based on the data reported by Boll et al. (2005), molecularly targeted strategies incorporating bortezomib with immunologic agents such as CD30 monoclonal antibodies may serve as a novel method to potentiate its efficacy in the clinical setting.

4.4.3 Targeted Immunotherapy Strategies

4.4.3.1 Epstein-Barr Virus Directed Therapy

Approximately 40–50% of cases of HL are associated with expression of Epstein-Barr virus (EBV) derived antigens in malignant H-RS cells and their variants. As a result, targeted immunotherapeutic approaches in EBV-specific malignancies including HL have been developed which incorporate adoptive transfer of EBV-specific cytotoxic T lymphocytes (CTL). In contrast to EBV-lymphoproliferative disorders (EBV-LPD), EBV-positive HL demonstrate type II latency characterized by the expression of a limited number of EBV-derived antigens, EBNA-1, LMP1, and LMP2, EBERs and BARTs which provide valid targets for immunotherapy. These antigens, however, are weakly immunogenic.

There is limited clinical experience using EBV-specific CTL in patients with recurrent/refractory HL. Autologous as well as allogeneic EBV-specific T cells have been developed and evaluated in patients with recurrent/refractory HL (Bollard et al. 2004; Gottschalk et al. 2005; Lucas et al. 2004). Autologous EBV-specific CTL generally have been shown to be well tolerated, persist for up to 12 months after infusion, exhibit a homing mechanism directed to the sites of tumor involvement and enhance EBV-specific immunity by expanding several logs in vivo after infusion and contributing to the memory pool (Bollard et al. 2004; Gottschalk et al. 2005). Biologic and antitumor activity was demonstrated. Reduction in viral load was observed suggesting biologic activity. Bollard et al. reported five patients with CR, one PR, and five SD in a series of 14 patients. Lucas et al. reported a series of six patients with matched or partially matched allogeneic EBV-specific CTL. Three patients were treated with CTL only (5×10^6 cells/kg) and experienced a partial response to therapy, with durable responses in two patients who were alive 6 and 22 months after infusion. Three patients were treated with fludarabine 30 mg/m^2 for 3 days followed by 1.5×10^7 cells/kg. Two of the three patients demonstrated partial responses, but it was unclear whether the response was due to fludarabine or CTL infusion. Persistence of donor CTL, however, was not demonstrated.

Overall, the results thus far indicate that the use of adoptive immunotherapy, although promising, is less effective in EBV-positive HL than in EBV-LPD. The lack of efficacy may be attributed to immunosuppressive factors secreted by H-RS cells or to the limitations of current methods utilized for the generation of EBV-specific CTL which may result in CTL lines that are dominated by clones reactive to viral proteins not expressed in HL. Thus, novel methods are being developed to enhance the potency of EBV-specific CTL by targeting CTL to subdominant EBV proteins (e.g., LMP1-specific, LMP2-specific) and by genetically modifying the expanded CTL to render them resistant to inhibitory cytokines or immunosuppressive medications.

4.4.3.2 Monoclonal Antibodies Targeting Receptors Expressed in HL

H/RS cells express several receptors that belong to the tumor necrosis factor (TNF) receptor family including CD30, CD40, and RANK. The CD30 receptor is selectively overexpressed in HL and thus is an excellent target for antibody-based immunotherapy. In a small subgroup of HL, CD20 is overexpressed at a high density over the surface of H/RS cells, rendering the antigen an excellent target for these patients. With the advent of a newer generation of chimeric and human monoclonal antibodies, the role of these agents in selective immunotherapy may be enhanced.

With the advent of chimeric human/mouse monoclonal antibodies directed toward the CD20 antigen (rituximab), successful salvage strategies have been developed for patients with recurrent lymphocyte predominant HL and other subtypes of CD20-positive HL either as monotherapy (Ekstrand et al. 2003; Rewald et al. 2003) or in combination with radiation therapy (Ibom et al. 2003; DeVita 2003). Rituximab has also been shown to sensitize lymphoma cell lines to cytotoxic agents. Recently, the use of rituximab for salvage therapy has been evaluated in a broader context in patients with recurrent classical HL, where CD20 is expressed in 20% of H/RS cells, to eradicate normal infiltrating B cells in an effort to deprive H/RS cells of important growth factors. Younes et al. postulated that eliminating $CD20^+$ bystander B cells might abort cytokine-mediated stimulation of H/RS cells (Younes et al. 2003). Benign infiltrating B cells in HL lesions can express CD40 ligand and CD30 ligand which may contribute to the survival of H/RS cells in vivo and may be involved in regulating cytokine and chemokine expression (Clodi et al. 2002; Gattei et al. 1997; Younes et al. 1996). A pilot study of six weekly doses of 375 mg/m^2 rituximab was conducted at MD Anderson Cancer Center in patients with classical HL irregardless of their CD20 expression in H/RS cells in order to selectively eliminate infiltrating B cells (Younes et al. 2003). Twenty-two patients were evaluable for response. Five patients (22%) achieved either a CR or PR with a median duration of response of 7.8 months (range 3.3–14.9 months). Responses were limited to nodal or splenic sites only and were associated with a decline in IL-6 cytokine levels in two patients with a PR. B symptoms resolved in six out of seven patients after therapy. Therefore, rituximab may have a potential therapeutic role in the treatment of patients with recurrent, classic HL limited to nodal sites and/or the spleen. Further studies are underway based upon these findings.

CD30 monoclonal antibodies have been evaluated extensively as a salvage approach in patients with recurrent/refractory HL; however, their efficacy has not been as promising as the results with rituximab. This has been largely due to the lack of efficacy demonstrated in HL patients with bulk disease at relapse. Recently, two monoclonal antibodies, the human 5F11 (Borchmann et al. 2003) and the humanized SGN-30 (Wahl et al. 2002), have exhibited in vitro cytotoxicity against HL-derived cell lines; however, limitations in sensitivity in clinical trials have been observed. Preclinical data suggest that limited sensitivity to CD30 monoclonal antibodies may be due to growth stimulation in $CD30^+$ HL through activation of NF-κB, an important antiapoptotic factor in HL, resulting in resistance to apoptosis after CD30 signaling. (Boll et al. 2005). The development of bispecific molecules such as anti-CD30/anti-CD64 reagent H22xKi-4 or the Ki-4 J 131 radioimmunoconjugate may abrogate this problem and warrant further investigation. Additionally, strategies incorporating anti-CD30 monoclonal antibodies in combination with targeted agents that suppress NF-κB activation, such as bortezomib, may also lead to more effective strategies to eradicate relapsed/refractory disease.

4.4.3.3 Radiolabeled Immunoglobulin Therapy in HL

Salvage approaches for HL have resulted in promising results with the introduction of radiolabeled immunoglobulin therapy RIT (Order 1988; Vriesendorp et al. 1991; Vriesendorp and Quadri 2000). The tumor-associated antigen used for RIT in HL has been ferritin, a high-molecular-weight protein present in the interstitium and cytoplasm (Eshbar et al .1974). Radiolabeled antiferritin targets tumor interstitium and shrinks tumors by radiation effects, not immunologic effects. Currently available radiolabeled antibody treatment has significant advantages over other systemic modalities of therapy for recurrent/relapsed HL. The advantages of radiolabeled antiferritin include: a higher therapeutic ratio than that observed in most phase I trials of chemotherapeutic agents because significant increases in tumor dose can be obtained without an increase in normal tissue toxicity; rare incidence of anti-antibody formation; lower cost; and absence of immunologic, pharmacologic or microbiologic complications in vivo. The predominant toxicity is bone marrow depression, particularly thrombocytopenia. More importantly, significant dose-response relationships to tumor remission have been reported with radioconjugates including ^{131}I antiferritin (40% PR) and ^{90}Y-labeled antiferritin (CR rates 50%). New developments in the stabilization of antibody fragments and design of labile linker chelates are expected to increase the radioisotope delivery to the tumor by monoclonal radioimmunoconjugates without jeopardizing the therapeutic ratio. Responses were more commonly reported in patients with smaller tumor volumes (<30 cm^3) and in patients with longer disease histories. In addition, a higher response rate was noted in patients who received dose 0.4 mCi ^{90}Y-labeled antiferritin/kg body weight. To date, limited data are available in children, and the safety must be established.

4.5 Future Considerations

As a better understanding is gleaned of the biology of HL, more effective approaches to the eradication of recurrent or refractory disease will be determined. Given that the Hodgkin/Reed Sternberg cells of HL aberrantly express the activated p50/p65 (Rel A) heterodimer for NF-κB, molecular targeting and inhibition of this pathway may prove to be valuable in the treatment of these patients. The focus of future retrieval approaches in pediatric patients with relapsed/refractory HL will incorporate novel agents (chemotherapeutic, biologic, and immunologic agents) and therapeutic strategies which act to perturb the NF-κB pathway through direct or indirect inhibition of NF-κB. Future challenges include the development of strategies to overcome resistance, minimization of short- and long-term toxicity, and the design of immunotherapy approaches to augment the immune response in an effort to improve the overall efficacy of these therapeutic strategies.

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