New drugs in the treatment of Hodgkin’s disease

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Summary

In the treatment of Hodgkin’s disease (HD) remission rates of 80% have been achieved with combination regimens such as COPP/ABVD; 30%–50% of these patients relapse, however, and less than 25% of those in first relapse can be cured. Although 90% of adults with advanced Hodgkin’s disease (HD) achieve a complete remission with new polychemotherapy regimens such as BEACOPP, it is too early to assess how many patients ultimately can be cured. In addition, these regimens are associated with severe side effects including infertility, cardiomyopathy or second malignancies. Thus, alternative strategies for improving the outcome of patients with HD have been developed. These approaches include new cytostatic drugs and biological agents. Here, we review the most recent developments including the new vinca alkaloid vinorelbine, the anthracycline idarubicin, the nitrogen mustard bendamustine, the recently developed nucleoside analogue gemcitabine, and immunotoxins against Hodgkin/Reed–Sternberg cells. We conclude that current polychemotherapy regimens could possibly be improved by introducing new agents with a different mechanism of action such as gemcitabine. In addition, some of these new drugs including gemcitabine or vinorelbine could contribute to the reduction of toxic side effects, thus resulting in an improved quality of life for patients with HD.

Key words: bendamustine, Hodgkin’s disease, gemcitabine, idarubicin, immunotherapy, vinorelbine

Introduction

In recent decades very effective polychemotherapy regimens for the treatment of Hodgkin’s disease (HD) have been developed. As a result, more than 70% of patients with HD can be cured with chemotherapy alone or in combination with radiotherapy [11]. In intermediate or advanced stage HD, alternating regimens such as COPP/ABVD can induce complete remission rates of about 80%. The German Hodgkin Lymphoma Study Group (GSHG) has recently reported that a new combination protocol, BEACOPP, induces 90% complete remissions in advanced stage HD [15]. Because these excellent results are being achieved with currently available cytostatic drugs, the introduction of new chemotherapeutic agents in the standard treatment regimens for HD patients need to be evaluated very carefully. Under these circumstances, analogues of parent compounds with improved therapeutic potential and reduced toxicity are of special interest. Therefore, this article focuses on the new vinca alkaloid vinorelbine, the anthracycline idarubicin, the nitrogen mustard bendamustine, and the recently developed nucleoside analogue gemcitabine. The introduction of new chemotherapeutical agents in the treatment of HD competes with the rapidly evolving immunotherapy. Since Hodgkin and Reed–Sternberg (HRS) cells are particularly suitable targets for selective immunotherapy, several approaches have been made during the last decade to overcome chemoresistance of HRS cells by immunological strategies. Here we also briefly summarize the most recent results of current approaches of monoclonal antibody-based immunotherapy in HD.

Vinorelbine

Vinorelbine (see Figure 1) belongs to the family of vinca alkaloids and is a semisynthetic analogue of vinblastine (5’Nor-anidro-vinblastine). The modification of the catharanthine moiety results in a high liposolubility and characteristic pharmacokinetic features. Like other vinca alkaloids, vinorelbine prevents the tubulin dimer polymerization by binding to the interpolar and mitotic microtubules during the G2 and M phases. In contrast
to its analogues, vinorelbine shows only little binding activity to axonal microtubules [3]. Thus, only minimal neurotoxicity at cytotoxic doses can be observed in clinical trials leading to a reduction of the deep tendon reflexes [10]. The main side effect of vinorelbine is myelosuppression, in particular neutropenia, without cumulative toxicity. Neutropenia WHO grade 3-4 occurs in up to 70% of patients, but is of very short duration with a low incidence of infectious complications [12]. Myelosuppression can be considerable and dose limiting if vinorelbine is used in combination regimens. Severe constipation is reported in less than 10% compared to about 30% treated with vincristine [13]. Administration by bolus injection in peripheral veins causes local venous toxicity in about 15% of patients. Mild vomiting, diarrhea, and alopecia are seen in less than 10% of patients. Thus, vinorelbine is generally well tolerated and has less pronounced side effects when compared to the known vinca alkaloids.

Vinorelbine used as a single agent therapy in HD was administered in all studies in a weekly schedule with 30 mg/m². Devizzi et al. report on 22 patients with HD refractory or resistant to at least two chemotherapy regimens, of which 50% (n = 11) showed an objective response (CR: n = 3, PR: n = 8) with a median duration of six months [12]. At least four courses of 30 mg/m² weekly were administered. Neutropenia grade 3 occurred in 53% with 13% grade 3 infections. These results are similar to those of Eghbali, who reports on 17 patients who had received at least two prior polychemotherapy regimens containing vinca alkaloids [16]. In 6 of 17 patients (35%) a partial remission could be documented with a median duration of 17 weeks. The main toxicity in these highly pretreated patients was leukopenia without infectious episodes. Neurotoxicity was not evaluated. Benchekroun et al. evaluated the response to vinorelbine in untreated patients with advanced HD [4]. Thirty-two patients received four weekly doses of vinorelbine prior to MOPP/ABVD chemotherapy, of which 30 patients were evaluable. Twenty-seven of 30 patients achieved a partial remission. Neutropenia was observed in 17 of 30 patients without infections. No neurotoxicity was documented. Vinorelbine has been used in the MINE polychemotherapy regimen in 100 patients for the salvage treatment of relapsed (n = 54, resistant relapse: n = 5) and refractory (n = 41) HD [20]. The MINE regimen consists of mitoguazone (500 mg/m², dl, 5), ifosfamide (1500 mg/m² dl−5), vinorelbine (15 mg/m² dl, 5), and etoposide (150 mg/m² dl−3). At least two courses at 28-day intervals were applied and followed by high-dose chemotherapy. With an overall response rate of 75% (CR: n = 34, PR: n = 39), this salvage regimen is very effective but was associated with severe myelosuppression and infectious episodes. Bonfante et al. report on 20 patients with relapsed or refractory HD treated with a combination of vinorelbine and ifosfamide [6]. The main toxicity was neutropenia (grade 3-4 in 50% of cycles, median duration of four days), but no data about remission rates have yet been published.

Idarubicin

Idarubicin (see Figure 2) is a semisynthetic drug that was first purified in 1976 [3]. Idarubicin differs from its parent drug daunorubicin only by the replacement of the C-4 methoxyl group in the D ring with a hydrogen atom. This modification has major consequences in the pharmacokinetic characteristics: idarubicin is much more lipophilic and can be administered orally. Its main metabolite idarubicinol is as active as the parent compound. In addition, idarubicin has shown greater cytotoxicity when compared with daunorubicin or doxorubicin in vitro [8, 14]. In clinical trials, idarubicin has proven activity against acute leukemias [33] and lymphomas [37]. Idarubicin exhibits less cardiotoxicity at equieffective doses compared with other anthracyclines, whereas hematotoxicity and mucositis appear to be more pronounced [28].

The GHSG is currently conducting a clinical phase-II study in which idarubicin (8 mg/m² dl, 2) is administered together with etoposide (60 mg/m² dl−4), ifosfamide (1000 mg/m² dl−4 continuous infusion), and dexamethasone (20 mg/m² dl−4) in patients with relapsed or refractory HD. G-CSF (Neupogen) is used to support neutrophil recovery (5 μg/kg daily). This regimen has previously shown promising activity in Non-Hodgkin’s lymphomas [18, 45]. The main toxicity was myelosuppression with leukopenia WHO grade 4 in 43 of 94 (45.7%, mean duration 2.9d) and thrombopenia WHO grade 4 in 26 of 94 (27.7%, mean duration 1.8d) courses. No other major non-hematological toxicity apart from alopecia was seen. Four patients with HD were included in the NHL study, of which three achieved a complete remission; all three had been refractory to prior chemotherapy.

Bendamustine

The nitrogen mustard bendamustine (see Figure 3) is a bifunctional alkylating agent that was developed in the early 1970s [42]. In vitro studies of its cytotoxic activity against human ovarian and breast carcinoma cell lines showed that bendamustine consistently induced more
DNA double-strand breaks than other alkylating agents including melphalan, cyclophosphamide or BCNU. Furthermore, there was no complete cross-resistance to the other alkylating drugs, suggesting a different interaction between bendamustine and DNA [50]. Administered as single agent, the dose-limiting side effect is leukopenia. After doses of 350 mg/m², leukopenia grade 3–4 was observed in 20% of patients [39]. Other side effects were mild with nausea and vomiting grade 1–2 in only 30% of patients and a more frequent transient general weakness. Bendamustine does not induce alopecia.

The clinical activity of bendamustine has been observed in various malignant lymphomas including low, intermediate, and high-grade NHL, chronic lymphocytic leukemia and multiple myeloma [7]. In HD three randomized studies were performed. In a phase II study, bendamustine was compared with cyclophosphamide monotherapy in untreated patients. Remission rates were 7 of 10 for bendamustine and 3 of 7 for cyclophosphamide [2]. Because of these encouraging results, bendamustine was introduced into the second-line therapy of HD in patients who were refractory to primary COPP (cyclophosphamide, vincristine, procarbazine, prednisone). Combined with daunorubicin, bleomycin and vincristine, bendamustine substituted the alkylating compound DTIC (DBVCRB). This regimen was compared to a modified ABVD (adriamycin, bleomycin, vincristine, DTIC) regimen in 73 patients and proved to be equieffective (RR: 68% vs. 83%). No significant differences in the duration of remission or median survival time were observed [26]. Subsequently, the DBVCRB regimen was tested in first-line therapy of advanced HD in a stratified randomized study, in which an alternating administration of DBVCRB and COPP was compared to COPP alone. Forty patients in each arm were treated and no significant difference in the remission rate (RR: 65% vs. 80%) could be observed [25]. However, the major problem with all the information gathered on bendamustine is that these data are not published in peer-reviewed journals since bendamustine had been developed and evaluated in the former German Democratic Republic (GDR).

Gemcitabine

Gemcitabine (see Figure 4) is a new pyrimidine antimetabolite with unique metabolic and mechanistic properties among the nucleoside analogues [44]. A special feature of gemcitabine is its ‘self-potentiating’ mechanism of action, resulting in enhanced accumulation and prolonged retention within malignant cells. In contrast to cytarabine, gemcitabine has shown excellent clinical activity in solid tumors [23, 41, 46]. Administered in a weekly schedule at a dosage of 1000 mg/m², side effects WHO grade 3 and 4 were myelosuppression (with neutropenia in 24%, anemia in 7.3% and thrombocytopenia in 4.7%) and an asymptomatic elevation of liver enzymes (GPT in 9.2% and GOT in 7.1%) [21]. Besides these toxicities, gemcitabine is well tolerated; in particular, nausea and vomiting occur in only 20% and alopecia in only 0.5%.

Because of the remarkable activity against solid tumors, gemcitabine was chosen for a multicenter clinical phase II study in patients with relapsed or refractory HD who had received at least two prior chemotherapies. Gemcitabine was administered at a dose of 1250 mg/m² on days 1, 8, and 15 every 28 days. An interim analysis of this ongoing trial showed an overall response rate of 53%, with 2 of 15 complete remissions and 6 of 15 partial remissions. Another six patients had stable disease. Myelosuppression was the main toxicity (thrombocytopenia grade 4: n = 1, anemia grade 3: n = 3, neutropenia grade 3: n = 5), but there was no evidence of any other organ toxicity or hair loss [51].

Immunotherapy

HD is a suitable target for immunotherapy for several reasons. The HRS cells express cell surface markers such as CD15 [29], IRac [30], CD25 [1], CD30 [49], CD40 [31] and CD80 (B7-1) [9], all of which are present only on a small minority of normal human cells. In addition, the number of malignant HRS cells is small. Furthermore, Hodgkin's lymphomas are well vascularized, thus allowing monoclonal antibodies (Moabs) or other immunocojugates easy access to their target. Although a great number of preclinical studies with different types of immunocojugates has been conducted, only few of these
new approaches have been evaluated in clinical studies (as reviewed by [48]).

Clinical experience exists with immunotoxins (ITs) consisting of monoclonal antibodies (Moabs) chemically linked to the deglycosylated A-chain (dgA) of ricin or saporin. One of these ITs termed RFT5.dgA is directed against the CD25 antigen (alpha chain of the high affinity IL-2 receptor). In severe combined immunodeficiency (SCID) mice with disseminated human Hodgkin's lymphoma, CRs were observed in 95% of animals after a single application of 8 μg of RFT5.dgA [52]. RFT5.dgA was subsequently selected for a phase I clinical trial in 15 patients with refractory HD [17]. Side effects were transient and related to the vasculature leak syndrome (VLS) with decreased serum albumin, edema, weight gain, hypotension, tachycardia, myalgia, and weakness. Responses included two PRs lasting over four and 18 months, one minor response, three stable disease and nine progressive disease. The maximal tolerated dose (MTD) was reached at 15 mg/m². This trial has been extended to a phase II study, but results are not published yet.

Another IT, containing Saporin-S6, was evaluated in a clinical trial. Saporin-S6 is a single-chain ribosome-inactivating protein (type 1 RIP) that was linked with the CD30 Moab Ber-H2 for use in HD. This IT showed promising activity in SCID mice with CD30+ lymphoma xenografts [43]. In this model, Ber-H2-Sap6 at doses of 3.3 μg/day for three days prevented tumor development in 79% of the animals treated, whereas 96% of untreated controls developed palpable tumors. In the clinical trial involving 12 patients with advanced refractory HD, 0.8 mg/kg Ber-H2-Sap6 was applied in one or two infusions over four hours. Four of these patients achieved PR and three had minor responses with a median duration of two months. The MTD of 0.8 mg/kg was established by grade 3 reversible vasculare leak syndrome and liver toxicity [19].

Another approach is the construction of bispecific monoclonal antibodies (Bi-Moabs) containing two different recognition sites for antigens on tumor cells and immunologic effector cells such as macrophages, T cells or NK cells [40]. Bi-Moabs activate cytotoxic effector cells at the tumor site via different target antigens such as CD2, CD3, TCR, CD16, CD28, CD32, or CD64. In HD, first results of a phase I–II study have been reported with HRS-3/A9, which is directed against the Fc(gamma)-receptor III (CD16 antigen) and the Hodgkin's-associated CD30 antigen, respectively [24]. Fifteen patients with refractory Hodgkin's disease were treated. HRS-3/A9 was administered four times every three to four days, starting with 1 mg/m². The maximum tolerated dose was not reached at 64 mg/m², but could not be escalated because of the limited amounts of HRS-3/A9 available. Toxicities were mild and consisted of fever, pain in involved lymph nodes, and a maculopapulous rash. A total of one complete and one partial remission (lasting six and three months, respectively), three minor responses (one to 11+ months) and one mixed response were achieved. A total of nine patients developed human antimouse Ig antibodies (HAMA), and four patients developed an allergic reaction after attempted retreatment. This study reflects the difficulties of immunotherapy with bispecific Moabs: the production of sufficient quantities of Bi-Moabs and the development of HAMA. Genetically engineered Bi-Moabs [32] may solve the problem of availability of sufficient Bi-Moabs. Induction of HAMA might be prevented by using diabodies [27] which consist of 'cross-over'-linked VH- and VL-chains of two different antibodies.

Discussion

Although 90% of adults with advanced HD can achieve a complete remission with new polychemotherapy regimens such as BEACOPP, it is too early to assess how many of them can ultimately be cured. With the previous generation of combination treatment, remission rates of 80% have been reported, but still 30%–50% of these patients relapse and less than 25% of those in first relapse can be cured [35, 36]. In addition, these regimens are associated with severe side effects including infertility, cardiac sequelae or second malignancies. Thus, alternative strategies have been developed to improve the outcome of patients with HD. These approaches include the development of new cytostatic drugs and biological agents with proven efficacy in preclinical models. In addition, there are numerous new chemotherapeutical drugs with excellent activity in other tumor entities, only very few of these drugs, however, have been evaluated in HD. One of the most promising new cytostatic compounds is the new vinca alkaloid vinorelbine, which has demonstrated activity in HD even in patients pretreated with vincristine and/or vinblastine. This efficacy seems similar to that achieved with polychemotherapy regimens [22, 47]. Moreover vinorelbine is well tolerated. Thus, the use of vinorelbine in first- and second-line therapy of HD in order to improve frequency and duration of response should be evaluated. Furthermore, this drug seems to be suitable as a single agent therapy in a palliative setting in patients with relapse after bone marrow transplantation (BMT), elderly patients or patients with a low performance status. The activity of vinca alkaloids under these circumstances has been shown for vinblastine providing effective palliation and may even be curative in selective patients with relapse after autologous BMT [34].

Anthracyclines belong to the group of the most effective drugs in the treatment of lymphoma and are well established in the treatment of HD. Among the anthracyclines, idarubicin is the only family member with an active metabolite (idarubicinol), resulting in a prolonged half-life and superior cytotoxicity [14]. Therefore, idarubicin is currently being investigated in a polychemotherapy regimen (DIZE) in relapsed or refractory advanced HD. The results are promising, but far too preliminary to assess the value of idarubicin in the treat-
ment of HD [45]. Since idarubicin causes severe side effects (hematotoxicity, cardiotoxicity, mucositis), its use will be restricted to patients who still have a curative option, e.g., for the induction of a complete remission prior to high-dose chemotherapy in those with sufficient hematopoietic capacity.

The nitrogen mustard derivative bendamustine is a bifunctional alkylating agent with a greater capacity of inducing DNA double-strand breaks in vitro than other alkylating drugs including BCNU, cyclophosphamide or melphalan. Bendamustine seems to have only partial cross-resistance with the other alkylating drugs [50] and has been associated with a low incidence of serious side effects. Dose-limiting toxicity is a reversible and not cumulative leukopenia. Nausea and vomiting are generally mild. Bendamustine does not induce hair loss. Furthermore, this new compound has proven its efficacy in lymphoma [7]. These features make bendamustine an interesting drug for the treatment of HD. Unfortunately, all the clinical trials in HD were conducted in the former GDR and are published in uncited journals. Although the results seem to show equieffectivity of bendamustine to cyclophosphamide or DTIC, there are no firm data available about the single agent activity of bendamustine in advanced refractory or relapsed HD. Thus, further clinical studies with bendamustine are warranted.

The pyrimidine analogue gemcitabine is the only drug currently under investigation that represents a new cytostatic mechanism of action. The ‘self-potentiating’ mechanism of action leads to an enhanced accumulation and prolonged retention of gemcitabine within the malignant cell [44]. In contrast to other nucleoside analogues, gemcitabine has proven activity against solid tumors. The drug is well tolerated with myelosuppression as the dose-limiting toxicity, but without any other severe organ toxicity or hair loss. The first and preliminary results of gemcitabine in advanced relapsed HD are promising, with an overall response rate of 53% in heavily pretreated patients [51]. If these results can be confirmed, gemcitabine must be evaluated in combination regimens.

As far as the rapidly evolving immunotherapy is concerned, the impressive experimental data have not been confirmed in early clinical trials thus far. Although some clinical efficacy has been demonstrated in clinical trials with immunotoxins and bispecific monoclonal antibodies, none of the currently available IT or Bi-Moab directed modifications of the IT and the development of humanized ITs or Bi-Moabs might optimize their efficacy and reduce their immunogenicity as it could be shown for the anti-CD25 Moab IDEC-C28B in low-grade NHL [38]. In the future, combining standard chemotheraphy with biological agents might result in the elimination of residual tumor cells and subsequently more relapse-free long-term survivors.

In summary, although some progress with immuno-therapeutical strategies has been made over the past decades, the search for the most promising approach still continues. Current polychemotherapy regimens in the treatment of HD could possibly be improved by introducing new agents with a different mechanism of action, such as gemcitabine, into combination regimens. In addition, some of these new drugs including gemcitabine or vinorelbine could contribute to the reduction of toxic side effects.

References

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