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Review paper

The role of vindesine in oncology—recommendations after 10 years' experience

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Vindesine, a vinca alkaloid derived from vinblastine, has been examined for activity against a variety of solid and hematological malignancies. Single-agent response rates average 18% in non-small cell lung cancer and it has been widely used in combination with cisplatin as first-line therapy for this disease. It has limited activity in breast cancer (average 16% response rate) and does not appear to improve outcome when combined with anthracyclines. Vindesine is frequently incorporated into combination regimens for the treatment of malignant melanoma, and head and neck cancer, although its single-agent activity in these diseases is modest (average 14 and 12% response rates, respectively). Its activity in the hematological malignancies appears to be greater and it has an important role in the treatment of acute lymphoblastic leukemia, particularly in children. It is currently being examined for its potential to synergize with the interferons and for its value as prolonged therapy in preventing metastasis.

Key words: Chemotherapy, leukemia, lung cancer, lymphoma, melanoma, vindesine.

Introduction

Vindesine sulfate entered clinical development in the late 1970s and early 1980s after the demonstration of a broad spectrum of activity in preclinical models and favorable toxicity profile in animal testing. It is now 10 years since vindesine became commercially available for the treatment of a variety of hematological and solid tumors, and this is perhaps an appropriate time to review the early data and the results of subsequent phase III trials in order to determine the current role for this agent in oncological practice.

Chemistry and pharmacokinetics

Vindesine (desacetyl vinblastine-amide sulfate) was synthesized from the naturally occurring parent compound, vinblastine, by alterations at the C-4 and C-23 positions.[1] Antitumor activity for all vinca alkaloids is similar and results from their high binding affinity for tubulin, the basic protein subunit of microtubules. Binding prevents polymerization of new microtubules and depolymerization of established microtubules resulting in cell cycle arrest, predominantly during the S phase.[2]

Detailed pharmacokinetic data are available for vindesine using a highly specific radioimmunoassay. Following i.v. bolus administration, the pharmacokinetics can be described by an open three-compartment model, similar to that of other vinca alkaloids, although there is large inter- and intra-patient variability of the pharmacokinetic parameters.[3] All vinca alkaloids have high distribution volumes indicating extensive tissue binding. Elimination half-lives of vindesine (24.2 h) and vinblastine (24.8 h) are significantly shorter than the terminal half-life of vincristine (85 h), and the resulting reduced duration of axonal exposure to drug probably explains the lower neurotoxicity of the former two compounds.[4] The main pathway for clearance of vindesine is via the hepatobilliary system and approximately 20% of the drug appears in the urine over 3 days.

The observation of very high initial serum levels of drug after bolus administration (well in excess of those necessary for therapeutic effect) has led to the suggestion that continuous infusion may be a logical schedule for this agent.[5] This could reduce toxicity by avoiding such high peak concentrations and increase the duration of exposure of cells to effective plasma levels. Early studies in hematological and selected solid tumors reported responses to continuous prolonged infusions of vindesine in patients who had experienced disease progression on bolus administration.[6] Plasma steady-state levels of 6–15 μg/l of vindesine (concentrations which produce

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mammalian tumor cell death in culture) can be achieved during prolonged administration with acceptable toxicity.[7]

Preclinical anticancer activity

A variety of animal and human tumor cell lines and xenografts were used to test the antiproliferative activity of vindesine and to compare it with other vinca alkaloids. Activity against Ridgeway osteosarcoma, Gardner lymphosarcoma and CA-755 mammary carcinoma was similar to that of vincristine and superior to vinblastine.[8] There was also evidence of activity against non-small cell lung cancer and gastric carcinoma (both for cell lines and human tumor xenografts) which was similar to vinblastine and superior to vincristine.[9] Activity of vindesine against P388 leukemia was 3-fold greater than for vincristine and 10-fold higher than for vinblastine.[10]

Phase I studies and toxicities of vindesine

Phase I studies with weekly bolus administration revealed dose-limiting toxicity to be neutropenia with a nadir on day 7–8.[11] Doses recommended for phase II studies were 3–4 mg/m^2/week in adults and 4–5 mg/m^2/week in children.[12] Alternative schedules examined have been administration daily for 2 or 5 consecutive days either as daily bolus injections or continuous infusions. Although the total weekly dose delivered by these schedules is greater (up to 10 mg/m^2), the dose-intensity is not increased as more prolonged neutropenia delays subsequent courses by up to 4 weeks.

Toxicity other than neutropenia is generally mild with vindesine. Thrombocytopenia is uncommon (paradoxically, increases in platelet counts have been reported to occur in up to 75% of patients). The incidence of alopecia varies widely between studies (reflecting differing durations of therapy and concommitant cytotoxics) but some degree of hair loss seems to occur in approximately half the patients treated, although it is rarely complete. Nausea occurs in 27% of patients but vomiting is uncommon. Mild neurotoxicity has been reported in up to 60% of patients after three or four courses of vindesine and is usually restricted to paresthesiae, although symptoms from autonomic neuropathy are occasionally seen.

Phase II/III trials with vindesine

Studies with vindesine in a wide variety of adult and pediatric hematological and solid tumors have been reported. A review of the literature relating to those malignancies for which there is greatest experience (lung, breast and head and neck cancer, malignant melanoma, leukemias, and lymphomas) is given below.

Lung cancer

Non-small cell lung cancer (NSCLC)—advanced disease

NSCLC is among the most chemoresistant of all malignancies. The only single agents which have been examined in large numbers of patients and shown reproducible response rates greater than 15% are cisplatin, mitomycin C, ifosfamide and vinorelbine.[13] The activity of single-agent vindesine in patients with NSCLC has been evaluated in several phase II studies.[14–22] The overall response rate was 18% (95% CI 13–22%)[23] and was consistent among the three major histologic subtypes of NSCLC. Activity appeared to be higher in previously untreated patients, with response rates of up to 25% and median survival of 14–29 months. The best results were obtained in studies when vindesine was given at a dose and schedule of 3–4 mg/m^2 weekly. After more than 30 years of clinical research, there is little consensus on the optimal combination chemotherapy regimen for advanced NSCLC. Methodologic inconsistency amongst clinical trials and, more importantly, the lack of highly effective chemotherapy have contributed to this confusion. In general, responses have been observed in less than 50% of patients and complete remissions are unusual. A recent meta-analysis demonstrated a significant, albeit modest, impact of cisplatin-based combination chemotherapy on survival as compared with supportive care[24] but did not identify which drugs should optimally be combined with cisplatin to achieve this effect. There is some evidence, however, that vindesine and cisplatin have synergistic antitumor activity[25] and 691 patients have been enrolled in eight trials of this combination.[26] An overall response rate of 26% (95% CI 25–33%) has been observed. Reported toxicities include myelosuppression, peripheral neuropathy, ototoxicity, vomiting and alopecia. The addition of one or two other drugs to this combination yields an increase in response rate without improving survival.[27–29] Reponse rate but not survival is improved with higher doses (100 mg/m^2 or greater) of cisplatin.[29,30] Thus vindesine and cisplatin can be considered one of the most active drug combinations in advanced NSCLC and it has become one of the most

frequently used two-drug combinations in this disease.

Several phase III trials have examined the role of vindesine in NSCLC. The majority have shown that vindesine improves the response rates of combination regimens but none have demonstrated a significant survival benefit. Two studies have, however, shown a significant response and survival benefit for the combination of vindesine and cisplatin compared to vindesine alone. In the first trial involving 105 untreated patients, response rates were 27 versus 6% and median survivals were 46 versus 17 weeks ($p = 0.008$).[31] In the second trial, vindesine and mitomycin C were equivalent to vindesine and cisplatin, and both were superior to vindesine alone in terms of response rate and survival.[32] The important question of whether the addition of vindesine to cisplatin improves outcome was assessed by randomizing 155 eligible patients to either cisplatin alone or cisplatin and vindesine.[33] There was a higher response rate for the combination arm (29 versus 12%, $p < 0.05$) but no significant improvement in median response duration or survival. Three studies have compared combinations of vindesine plus cisplatin against supportive care. Two of these demonstrated a significant but modest survival advantage for patients receiving chemotherapy[34,35] and, in the third, the median survival was longer in the chemotherapy arm although the difference was not statistically significant.[36]

Further information on the activity of vindesine in NSCLC is obtained from randomized trials comparing combination chemotherapy regimens with substitution of vindesine by other drugs. Vindesine with mitomycin C was equivalent to ifosfamide and mitomycin C with respect to response rate and survival, and was associated with significantly less toxicity.[37] Vindesine was compared with vinblastine in combination with cisplatin and the results indicated a non-significant trend towards a higher response rate in the vinblastine arm and towards longer duration of response for the vindesine combination.[38] Severe leucopenia was more frequent in the vinblastine arm. Four studies have shown that vindesine and cisplatin is as active as etoposide and cisplatin, in terms of response rate and survival,[27,28,39,40] although it was associated with more frequent granulocytopenia and peripheral neuropathy. In a recently reported well-designed three-arm study comparing cisplatin with either vinorelbine or vindesine and single-agent vinorelbine, both higher response rate and longer survival were observed with vinorelbine and cisplatin compared to vindesine and cisplatin (median survival duration, 40 versus 32 weeks, $p = 0.04$; median response rate 30 versus 19%, $p = 0.02$). The response rate and a median survival in the single-agent vinorelbine arm were both lower (14% and 31 weeks, respectively) than for either of the combinations. Grade 3 and 4 neutropenia occurred significantly more frequently in the vinorelbine arm while severe neurotoxicity was more common with the combination of vindesine and cisplatin.[41]

NSCLC—neoadjuvant therapy

The use of neoadjuvant chemotherapy for locally advanced disease may become the most significant development in the management of NSCLC in many years. There are several potential theoretical benefits from this approach including control of systemic disease before the development of resistance, improved delivery of chemotherapy to tumor cells before alteration of tumor vasculature from surgical manipulation, continuation of a regimen proven to be effective after pathological examination of the resected specimen and facilitation of complete resection if downstaging occurs. An overall response rate of greater than 50% has occurred during pilot studies involving neoadjuvant therapy.[42] Approximately 70% of patients on these trials were offered surgery and complete resection was possible in 60%, although fewer than 10% had achieved pathologic complete responses. Median survival ranged from 8 to 31 months, with 2–3 year survival rates of approximately 30%. The combination of mitomycin C, vindesine and cisplatin appears to be one of the most active regimens in phase II trials in this setting. The overall response rate in patients with N2 disease (mediastinoscopy staged) was 71% and the resection rate was 51%. The median survival was 21.3 months with a 6 year survival rate of 29% for all patients (the corresponding figures for those undergoing complete resection were 32.4 months and 40%).[43,44]

Only recently have randomized trials examining the benefit of neoadjuvant chemotherapy been instituted and provocative results are available from three. The chemotherapy regimens used were mitomycin C, ifosfamide, cisplatin,[45] cyclophosphamide, etoposide, cisplatin[46] and etoposide, cisplatin,[47] and these were compared with surgery alone or surgery plus radiotherapy. Interim analyses in two studies showed significant survival benefits for the neoadjuvant arms (median survival: 26 versus 8 months and 64 versus 11 months) leading to premature closures of the studies.[45,46] The third trial

showed a trend toward improved median survival (28.7 versus 15.6 months).[47] The magnitude of the improvement with combined modality therapy is not entirely consistent with previous data and early termination of the studies might have biased estimates of the treatment effect. However the results are interesting and provide a strong rationale for continuing to examine neoadjuvant therapy for patients with locally advanced NSCLC. Although pilot studies of neoadjuvant vindesine and cisplatin in stage IIIA NSCLC have been promising, its true value remains to be defined in phase III trials.

Small cell lung cancer (SCLC)

There are no reported single-agent phase II studies of vindesine in SCLC. In a relatively small phase III trial, 116 patients received cyclophosphamide with either vincristine or vindesine.[48] There was no significant difference in response rate, median duration of remission, median survival or 2 year survival. In a second phase III trial, 221 patients were randomized to etoposide and vindesine (EV) or the same combination with cisplatin (CEV). The addition of cisplatin resulted in a significant increase in objective response rate (74 versus 55%; $p=0.01$) without a significant improvement in survival.[49] Median survivals for EV and CEV were 40 and 45 weeks, and 2 year survivals were 11 and 9%, respectively. Vindesine has been a component of two dose intensive polychemotherapy studies but the results of such an approach do not appear to be superior to standard therapy and are associated with significant toxicity.[50,51] Although the designs of the studies reported to date do not enable a clear determination of the impact of vindesine on the results of treatment of SCLC, there does not appear to be an advantage to adding this drug to standard treatment.

Breast cancer

Phase II trials of vindesine in patients with breast cancer have investigated several schedules: single dose weekly[52–57] and biweekly,[58] daily for 5 days every 4 weeks,[59] and 72 h[60] or 120 h[58] continuous i.v. infusion every 21 days. The greatest experience is with the weekly schedule. In six trials testing a dose of 3–4 mg/m^2 weekly, the response rate in heavily pretreated patients ranged from 0 to 29% (average of 16%). Responses were seen in patients who were refractory to other vinca alkaloids and to anthracyclines.

Several phase II studies have examined the activity of vindesine in combination regimens. With mitomycin C response rates varied widely from 0–40%.[61–63] In a non-randomized study, previously treated patients received either vindesine or vinblastine with mitomycin C.[64] Objective responses were seen in six of 15 patients and seven of 22 patients, respectively, suggesting that the two analogs have similar activity in this disease. Although results of phase II studies are not directly comparable, the addition of mitoxantrone to vindesine/mitomycin C does not seem to dramatically improve the response rate in pretreated patients. This three drug combination resulted in a response rate of 19.2% (95% CI 12–30%) in 103 patients who had received prior chemotherapy which included anthracyclines.[65]

Randomized trials have shown that the combination of vindesine plus epirubicin is equivalent to vindesine and mitoxantrone,[66] and that three drug combinations containing vindesine and cyclophosphamide with either doxorubicin or mitoxantrone[67] produce similar response rates and survival. Unfortunately, however, the addition of vindesine to epirubicin in a randomized trial involving 103 anthracycline-naive patients failed to improve the response rate, median time to progression or median survival suggesting that its role, if any, is limited in anthracycline based combinations.[68]

Head and neck cancer

Chemotherapy is offered to palliate symptoms in patients with recurrent or metastatic head and neck carcinoma. Single agents used in this setting include 5-fluorouracil (5-FU), methotrexate and cisplatin. All have demonstrated partial response rates of 30% or less.[69–71] The median duration of response ranges from 3 to 6 months and median overall survival is 6–10 months. Combination regimens result in higher response rates with no improvement in overall survival and significantly greater toxicity compared with single-agent therapy.[70,71]

Response rates to vindesine in single-agent phase II studies have varied from 0% in previously treated patients to 25% in chemotherapy-naive patients.[72–76] The heterogeneity of patients included in these trials makes it difficult to draw firm conclusions, but results suggest that vindesine has real, albeit limited activity in this disease.

The highest response rates reported in phase II trials of vindesine have occurred when it has been included in cisplatin-containing regimens. Objec-

tive responses were seen in 17 of 27 evaluable patients (63%) with three complete remissions (11%) with cisplatin, vindesine and mitomycin C.[77] In 31 previously untreated patients with metastatic disease who received vindesine given as a 96 h continuous i.v. infusion and cisplatin, an overall response rate of 52% (16% CRs) was seen.[78] The median durations of complete and partial remissions were 6.4 and 4.4 months, respectively. The combination of cisplatin, vindesine and 96-h continuous infusion of 5-FU in untreated patients with locally advanced disease was associated with a response rate of 76% and median survival of 14 months in 29 evaluable patients. In these trials, the major toxicity was leukopenia. Overall, these results are comparable to other cisplatin containing combinations.

Neoadjuvant or induction chemotherapy is being investigated in patients with advanced stage head and neck cancer to reduce tumor burden and thus facilitate organ preservation prior to definitive local treatment. To date, neoadjuvant chemotherapy has been beneficial in decreasing the incidence of distant metastases yet no survival advantage has been demonstrated in four randomized trials.[79–82]

Vindesine has been used as part of two induction regimens investigated in sequential randomized trials at the Institute Curie.[83] Two hundred and eight patients with advanced T3 and T4 head and neck carcinomas were selected randomly to receive local therapy with or without prior induction chemotherapy. The two chemotherapy regimens used were: (1) cisplatin, bleomycin, vindesine, mitomycin C and methylprednisolone for two cycles followed by local therapy; or (2) cisplatin, 5-FU and vindesine for a total of three cycles followed by local therapy. Both the number of complete and partial responses were higher for the second treatment group (CR rate 22 versus 10%, PR rate 48 versus 40%). The difference in response rate may be explained by the additional cycle of chemotherapy. Although there was no overall survival advantage or improvement in local control with induction chemotherapy, a significant decrease in distant metastases was seen when the data from the two treatment groups were combined.

Malignant melanoma

Early phase II studies in malignant melanoma suggested that vindesine may be one of the few cytotoxic agents which have activity in this disease. In the largest study, which included 56 patients, Retsas *et al.* reported a 20% response rate with two complete remissions.[84] Although the median response duration was only 8 weeks, some durable responses occurred (up to 3 years). Seven other phase II studies using weekly bolus vindesine have included over 200 patients (the majority having received prior chemotherapy) and the mean response rate was 14%.[85–91] One trial utilized a 5 day continuous infusion with only two of 31 patients (6%) responding.

Several studies have investigated vindesine in combination regimens. Retsas *et al.* combined DTIC with vindesine in 44 patients and observed five complete and five partial remissions (overall response rate 22%) with a median response duration of 20 weeks.[92] The second phase II study combined vindesine with cisplatin and produced a 30% response rate (two complete remissions) among 40 patients.[93] Subsequent randomized phase III trials have attempted to identify the optimal regimen in this disease. Ringborg *et al.* compared single-agent dacarbazine with dacarbazine and vindesine in 119 patients.[94] Response rates in the single-agent and combination arms were 18 and 25%, respectively and the corresponding median response durations were 123 and 171 days. Both of these suggest a trend for improved outcome for the addition of vindesine to DTIC although the differences failed to reach levels of significance. Two studies have examined three-drug combinations. In the first, procarbazine and lomustine were combined with either vindesine or dacarbazine in 43 patients.[95] The response rate was higher in the dacarbazine arm (36 versus 24%) but this was at the cost of significantly greater toxicity. The numbers of patients were too small to draw any meaningful conclusions about efficacy. The second study compared vindesine and cisplatin with either etoposide or lomustine.[96] Response rates in the etoposide and lomustine arms were 31 and 20%, respectively, but again too few patients were included to determine the optimal regimen. Two interesting recently reported studies have included biological agents with chemotherapy. A South African trial compared single-agent vindesine with vindesine plus interferon-α and interferon alone in 60 patients.[97] The response rate (40%) was significantly higher and survival (median 19 months) was greater for the combination arm suggesting synergy between the two agents. A second study from the MD Anderson examined the potential value of a BCG extract to improve outcome of the combination of vindesine and dacarbazine.[98] Response rates among the 103 patients

entered with or without the extract were 17 and 16%, respectively. Survival was also not affected.

Leukemia

A large proportion of the early trials with vindesine investigated its potential role in acute lymphoblastic leukemia (ALL). Single-agent response rates have varied between 5 and 63% with an average of 38% (15% CR) among 93 patients reported.[99–102] Activity appears to be unaffected by the concommitant use of steroids but is generally higher in children (41%) than adults. This figure is encouraging as the majority of patients included were refractory to prior therapy and compares favorably with single-agent activity of vincristine of 40–50% in non-pretreated patients. Of interest is the suggestion from a French study that there may be non-cross-resistance between vincristine and vindesine.[103] Of those patients who had progressed during vincristine, 47% subsequently responded to vindesine. Of those who had previously responded to vincristine-containing regimens, 67% responded to subsequent vindesine at the time of relapse.

Several combination regimens incorporating vindesine in ALL have been reported. The CCSG compared asparaginase and prednisolone with either vindesine or vincristine in relapsed children and revealed identical results for those who were not primarily refractory to induction therapy with 57% complete remissions in both arms.[104] For children in second or subsequent relapses, the vindesine arm appeared superior with a 50% complete response rate compared with a 35% CR rate in the vincristine arm. A phase II study combining vindesine, daunorubicin and prednisone in 38 patients with resistant or refractory ALL produced a complete remission rate of 51% of those in first relapse and 25% of those in second or later relapses, figures which were felt to be similar to those achieved historically in the same institutions using vincristine in combination.[105] In a recent publication from the Pediatric Oncology Group, 39 children in first relapse (but presumed to be vincristine-sensitive) were randomized to vincristine or vindesine plus prednisone;[106] 55% in the vindesine arm and 37% in the vincristine arm achieved complete remissions, although toxicity was felt to be greater in the former.

Unfortunately no large studies have been reported using vindesine as first-line therapy in ALL. Given the high activity with established regimens, it would be difficult to show a significant advantage for a new combination in terms of response rate but comparisons in terms of toxicity, response durations and survival could be of interest.

The activity of vindesine in acute and chronic myeloid leukaemia (AML and CML) has been examined in several small series (reviewed in Cersosimo *et al.*[107]). Although reductions in blast cell populations were frequently reported following single-agent vindesine in AML, true responses occurred in less than 10% of patients. In contrast, vindesine appears to have useful activity in CML patients with blast cell crisis. Of a total of 83 patients who received vindesine (with or without prednisone) in seven studies, 41 (49%) achieved a complete or partial remission.[108–112] The addition of cytosine arabinoside to vindesine and prednisolone was examined in 21 patients and appeared to be well tolerated.[113] A complete remission was seen in 15 patients (71%).

Hodgkin's disease and non-Hodgkin's lymphoma

The activity of single agent vindesine in Hodgkin's disease was examined in a large phase II study at the Memorial Sloan Kettering which included 42 heavily pretreated patients.[114] Seven partial remissions were observed. Several other broad phase II trials have included patients with relapsed Hodgkin's disease and the overall reponse rate among 62 patients was 19% (reviewed by Raich *et al.*[115]). One small pilot study combined vindesine with doxorubicin, prednisone and carmustine, and obtained remissions in all 10 pretreated patients with two complete responses. This was higher than the 56% response rate which was previously seen by the same group when vincristine had been used in this combination.[116] Several small studies using a variety of combination regimens which include vindesine have been reported in the literature but it is impossible to determine the contribution which this agent has made to the activity. Unfortunately no randomized studies have been reported which compare the activity of the different vinca alkaloids as first-line therapy in this disease.

Single-agent vindesine has been given to 110 patients with relapsed non-Hodgkin's lymphoma predominantly as part of broad phase II studies (reviewed by Hellmann and Carter[117]). The overall response rate was 45% with nine complete remissions. Several studies have included vindesine as part of a combination regimen in relapsed high grade disease and activity has been 40–50%.[118] It is impossible to determine the role of vindesine in

such small studies as similar response rates are seen with a wide variety of combinations in this setting. The French LNH-84 regimen comprising doxorubicin, vindesine, cyclophosphamide, bleomycin and prednisolone has been used as first-line therapy in high and intermediate grade non-Hodgkin's lymphoma in 737 patients and has one of the highest reponse rates reported with a 75% complete remission rate.[119] Two year survival rates were also impressive at 67% but it is difficult to attribute this solely to the induction regimen as patients went on to receive high-dose intensification. One study included 57 patients with newly diagnosed high-grade lymphoma and randomized them to receive CHOP (cyclophosphamide, vincristine, doxorubicin and prednisone) or MEVP (mitoxantrone, etoposide, vindesine and prednisone).[120] The complete response rate to MEVP was 63% (3 year relapse-free and overall survivals were 46 and 59%, respectively). The results were similar for both arms, although myelosuppression was greater following MEVP. Again it is difficult to assess the role of vindesine from this study as the other cytotoxic agents used were different in the two arms.

Discussion

The vinca alkaloids have a long-established role in adult and pediatric oncology practice, predominantly as part of combination chemotherapy regimens used to treat a broad spectrum of tumor types. The clinical development of vindesine was based on encouraging preclinical findings suggesting antiproliferative activity in a variety of solid and hematological tumor models which appeared to be broader than for either vincristine or vinblastine. It was also anticipated that the neurotoxicity and myelosuppression seen with vincristine and vinblastine respectively might be lower with vindesine. Does the clinical experience support these anticipated benefits?

Early studies suggested activity in a variety of tumor types, with a spectrum which did appear greater than had been seen with vincristine and vinblastine (although screening during early development of the latter agents was far less comprehensive). Of considerable interest was an average response rate of 18% in NSCLC which led to phase II studies incorporating vindesine in a variety of combinations. Cisplatin and vindesine are one of the most widely used combinations in this disease, and experience in many studies suggests a reproducible response rate of approximately 26%. It is clear from randomized studies that this is higher than for single-agent vindesine, and one prospective study has demonstrated the combination to be superior to single-agent cisplatin. Important data on the use of combination chemotherapy suggest that there is a modest survival benefit when cisplatin-containing regimens (which have usually included vindesine) are compared with 'best supportive care' in advanced NSCLC and there is increasing optimism that similar regimens may improve outcome when given in the neoadjuvant setting prior to surgery in early stage disease. With the recent availability of vinorelbine, however, and the demonstration of a higher response rate and survival for its use in combination with cisplatin than for cisplatin and vindesine, the future role of vindesine as first-line chemotherapy in NSCLC may be reduced if the findings of the initial trial are confirmed. From the very limited literature on the use of vindesine in SCLC, there does not appear to be a clear role for its incorporation into cytotoxic regimens in this disease.

Experience with the use of vindesine in breast cancer suggests that it has modest activity which is probably similar to that of the other vinca alkaloids in advanced disease. It does not appear to improve outcome when added to anthracyclines as first-line therapy and its role, if any, is therefore limited to relapsed disease as part of novel combination regimens.

As a result of its relative lack of toxicity, vindesine has been fairly extensively used in patients with head and neck cancer, a group which normally tolerates chemotherapy poorly. Its single-agent response rate of approximately 25% makes it one of the more active drugs in previously untreated disease. It is frequently used in combination with cisplatin (often with additional 5-FU or mitomycin C) for the treatment of advanced disease and may find an increasing role in neoadjuvant therapy of this disease if the early promise with this approach is confirmed by ongoing studies.

Vindesine was frequently used in patients with malignant melanoma after encouraging data from early phase II studies suggested it to be one of very few agents with greater than 15% activity in this disease. It would appear that its combination with one other cytotoxic drug (most frequently dacarbazine or cisplatin) increases response but at the expense of greater toxicity. The increasing trend towards the use of biological agents in this disease has reduced the role of chemotherapy although the encouraging results of the South African study combining interferon-α and vindesine warrants further investigation.

Vindesine has been investigated in all forms of hematological malignancy. Its main role would appear to be in the treatment of the leukemias—particularly in combination regimens for ALL in children. It is among the most active single agents in relapsed disease and there is some evidence to suggest activity in patients whose disease was refractory to other vinca alkaloids. Although it has minimal activity in acute myeloid leukaemia, its use in CML is associated with high response rates during blast cell crisis. Although the interferons, retinoids and transplantation are increasingly employed as first-line therapy in this disease, the use of vindesine at the time of relapse may provide useful palliation of symptoms with minimal toxicity. The activity of vindesine in Hodgkin's disease and the non-Hodgkin's lymphomas would appear to be comparable with that of vincristine and vinblastine but its use in combination is limited to very few studies and there is no evidence currently available to support its routine use as first-line therapy in these diseases.

Conclusions

As predicted from preclinical testing, vindesine has a broad spectrum of activity against a variety of solid and hematological malignancies. However, unfortunately, much of the early promise for its use in the common solid tumors (particularly breast and lung) has not been borne out by subsequent experience during randomized clinical trials when its addition to established regimens or substitution for another agent has not yielded superior results and has often added to toxicity. Nevertheless, its use with cisplatin in NSCLC remains one of the standard regimens for the treatment of this disease. It is one of the few agents with activity in melanoma and head and neck cancer, and its use alone or in combination may be justifiable in selected cases for the palliation of symptoms. Vindesine would appear to have an important role as an alternative to vincristine in combination therapy regimens of the treatment of ALL. There are several questions still to be answered for this agent. It will be important to confirm the interesting observation of its possible synergy with interferon. Suggestions that it may have antimetastatic properties[121] led to a study which recently demonstrated that chronic administration (up to 7 years) was feasible and may have reduced recurrence rates in a variety of malignancies by preventing systemic relapse.[122] Although clinical trials have demonstrated a relatively modest role for vindesine as first-line therapy in the majority of malignancies, these new findings, if confirmed, could have an impact on its future value in cancer medicine.

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