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Oral Chemotherapy Agents in the Treatment of Leukaemia

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Abstract

Oral chemotherapy agents have been an important component of the treatment of leukaemia for many years. Obstacles such as poor or erratic bioavailability and noncompliance have often limited the utility of oral agents in the treatment of leukaemia. However, recent evaluations of new or existing oral agents have expanded the clinician's options and understanding of the use of these drugs in the treatment of leukaemia. One major advance is the use of tretinoin (all-*trans* retinoic acid) in the treatment of acute promyelocytic leukaemia (APL). Tretinoin, an oral vitamin A derivative that reverses abnormal differentiation in APL is now an essential component of first-line therapy for APL, replacing standard intravenous chemotherapy induction regimens. Other advances include an increased understanding of the pharmacokinetic and pharmacodynamic profile of oral chemotherapy agents such as etoposide and high dose busulfan, allowing for modifications or individualisation of administration regimens to enhance efficacy or minimise toxicity. Evaluations of noncompliance with oral agents in the treatment of leukaemia have also provided the clinician with important information on how this obstacle to oral therapy may be overcome or minimised.

Oral chemotherapy agents have been an essential component of the treatment of leukaemia, particularly chronic leukaemias, for many years. Oral agents such as busulfan, hydroxycarbamide (hydroxyurea), chlorambucil, and prednisone have long been used as standard treatments for chronic myelogenous leukaemia (CML) and chronic lymphocytic leukaemia (CLL). During the past several years, there has been a renewed interest in the use and development of oral chemotherapy agents in the treatment of leukaemia. The oral agent tretinoin (all-*trans* retinoic acid) has markedly changed the clinician's approach to the treatment of acute promyelocytic leukaemia (APL). Orally administered tretinoin is now part of first-line induction therapy for this subclass of acute myelogenous leukaemia (AML).

Other evidence of a renewed interest in the use of oral chemotherapy is the increased volume of clinical trials with orally administered agents. Recent investigations have attempted the following: to better define the pharmacokinetic and pharmacodynamic profiles of various chemotherapy agents after oral administration; to understand the issues surrounding, and improve upon, patient compliance with orally administered agents; and to explore new oral formulations with the aim of improving efficacy and/or decreasing toxicity. Numerous factors have influenced this renewed interest in oral chemotherapy, but major factors include potential pharmacoeconomic advantages of oral

agents over intravenous agents and potentially enhanced quality of life. Table I lists various oral chemotherapy agents, their application in the treatment of leukaemia, and recent investigations of the use of these agents to treat these diseases.

1. Advantages and Disadvantages of Oral Chemotherapy Agents

Just as the clinician must consider certain issues when prescribing intravenous therapy, such as appropriate scheduling based on pharmacokinetic and pharmacodynamic properties and obtaining intravenous access, other issues such as bioavailability and compliance must also be considered when prescribing oral therapy as part of cancer treatment. Pharmacokinetic variations of oral agents, particularly with respect to bioavailability, have historically limited the application of these agents in cancer patients. Erratic absorption occurs with numerous commonly used drugs. The bioavailability profiles of drugs such as aciclovir and cyclosporin, which are often unpredictable in the general patient population, may be even more erratic in cancer patients.[1,2] Such drugs may require periods of intravenous administration in order to ensure that plasma concentrations are sufficient to achieve the desired therapeutic effect.[2]

In general, intestinal absorption and enterohepatic metabolism pathways control the degree of bioavailability of an oral agent.[3] In cancer patients, the pharmacokinetic profile of etoposide demonstrates the variability of absorption that may be seen with oral chemotherapy agents and must be considered when prescribing oral agents to treat leukaemia. For example, etoposide exhibits saturable absorption, a property that can influence the degree of absorption and may influence the expected outcome observed at various doses. At lower dosages of oral etoposide (100 mg/day), bioavailability is approximately 75%; at higher dosages (400 mg/day), this decreases to approximately 45%.[4] A linear increase in bioavailability has been described for doses up to 200mg, with saturable absorption kinetics observed at higher doses.[5] Thus, it is most likely that higher doses of oral etoposide will not provide additional benefit compared with lower doses because of the relatively similar patient exposures between doses. Absorption may also be limited by variations in the stability of oral agents at gastric or intestinal pH, which should be considered when prescribing oral agents to cancer patients.

Intestinal metabolic pathways such as the intestinal cytochrome P450 (CYP) system, particularly

Table I. Oral agents for treatment of leukaemia

Oral agent	Clinical applications	Recent investigations and advances
Tretinoin	Acute promyelocytic leukaemia	Superior outcome when compared with intravenous chemotherapy; now considered standard first-line therapy
Busulfan	BMT (high dose)	Alterations in pharmacokinetic and pharmacodynamic profile evaluated; administration strategy modified on the basis of age and, potentially, individual exposure
Chlorambucil	Chronic lymphocytic leukaemia	Recently compared to purine analogues as first-line or salvage therapy
Cladribine	Chronic lymphocytic leukaemia	Oral route of administration recently evaluated as first-line therapy
Etoposide	Acute myelogenous leukaemia	Etoposide phosphate formulation associated with higher bioavailability than conventional formulation
Hydroxycarbamide (hydroxyurea)	Chronic myelogenous leukaemia	Associated with superior outcome when used as pre-BMT therapy compared with busulfan pre-BMT therapy
Idarubicin	Acute myelogenous leukaemia	When combined with oral etoposide, may provide treatment alternative for elderly patients ineligible for aggressive intravenous induction therapy
Mercaptopurine	Acute lymphocytic leukaemia	Compliance monitoring and improvement strategies under evaluation; evening administration schedule preferred
Methotrexate	Acute lymphocytic leukaemia	Oral route preferred for prolonged maintenance therapy; evening administration schedule preferred
Thioguanine	Acute lymphocytic leukaemia	Compliance monitoring and improvement strategies under investigation

BMT = bone marrow transplantation.

CYP3A4, may also influence the bioavailability of orally administered drugs. Oral chemotherapy agents metabolised via the CYP system are subject to drug interactions that may significantly influence bioavailability and potential response to therapy. CYP3A4 is the major component of the intestinal P450 system and has been documented to play a role in the altered absorption of various drugs used in cancer patients.[3] Noted examples of this interaction are the ability of CYP enzyme inducers, such as rifampicin (rifampin), to decrease the absorption of cyclosporin, and of inhibitors, such as fluconazole, to increase the absorption of cyclosporin.[6,7] Such interactions can be clinically significant, requiring therapeutic drug monitoring and dose modifications. Etoposide is also metabolised by the CYP3A4 system. When etoposide is coadministered orally with ketoconazole, a CYP3A4 inhibitor, the area under the plasma concentration-time curve (AUC) for etoposide is reported to increase by 44%, demonstrating enhanced absorption due to blocked intestinal metabolism of etoposide.[8]

In addition to the pharmacokinetic and pharmacodynamic properties of oral chemotherapy agents, other less tangible properties may also substantially influence the applicability of these agents. Compliance with orally prescribed regimens has been studied in various cancer patient populations. In 12 patients with small cell lung cancer who were receiving low dose oral etoposide on an outpatient basis, the overall compliance rate for the 25 treatment periods was found to be 93%.[9] Noncompliance among paediatric patients with acute lymphocytic leukaemia (ALL) has been noted to be as high as 30%, and may be a substantial contributing factor to late relapses observed in this disease.[10] New approaches such as electronic monitoring of pill taking have been used to document and improve compliance with oral agents.[11-13] Other strategies documented to enhance compliance with oral agents include patient education, pill-taking exercises, and psychological support.[10,14]

When selecting treatment for cancer patients, pharmacoeconomic issues should also be addressed if oral or intravenous routes of administration are considered. Pharmacoeconomic evaluations of this issue have been conducted in populations other than cancer patients. In a comparison of oral versus intravenous ganciclovir in AIDS patients, the mean total cost of therapy for oral administration was approximately one-third less than the cost of intravenous therapy, which included the cost of administration time, infusion pumps, and central venous catheter placement and management.[15] Similar cost savings could be envisioned in cancer patient populations, particularly if the patient could avoid hospitalisation or long clinic visits for administration of intravenous therapy. Of course, before substituting the oral route of administration for the intravenous route on the basis of cost savings, possible effects on efficacy, toxicity, and quality of life should be considered.

Patient preference and quality of life must also be considered when selecting the route of administration for a particular patient's therapy. In a study addressing patient preference in treatment options of advanced malignancies, >90% of patients stated they would prefer oral over intravenous administration if the 2 routes were similar in efficacy and onset of response.[16] Convenience, patient control over their own environment, and lack of need for intravenous access all contributed to this preference. In addition, in the setting of palliative therapy, orally administered drugs that enhance or help maintain quality of life will most often provide the best option for patients.

2. Current Status of Oral Treatment of AML

In general, the role of oral chemotherapy in the treatment of AML has been limited. Agents such as etoposide may be administered orally for palliative therapy in multiply-relapsed or refractory patients, or in those unable to tolerate aggressive intravenous regimens. Hydroxycarbamide may be used in patients who present with leucocytosis to initially decrease the white blood cell count and reduce the leukaemic burden. More recently, the introduction

Table II. Use of tretinoin either alone or in combination with chemotherapy for induction of response in newly diagnosed acute promyelocytic leukaemia

Reference	No. of patients	Total CR (%)	Tretinoin alone (%)	Tretinoin + chemotherapy[a] (%)
Huang et al. [29]	16	16 (100)	16 (100)	
Fenaux et al.[30]	26	25 (96)	14 (54)	11 (42)
Fenaux et al.[31]	54	49 (91)	14 (26)	35 (65)
Kanamaru et al.[32]	109	97 (89)	25 (23)	72 (66)
Avvisati et al.[33]	20	18 (90)		18 (90)
Mandelli et al.[34]	240	229 (95)		229 (95)
Tallman et al.[35]	172	124 (72)	124 (27)	

a Values reflect percentage of total number of patients receiving tretinoin.
CR = complete response.

of the oral differentiating agent tretinoin has changed the approach to treatment of APL.

2.1 Use of Tretinoin in the Treatment of APL

Advances in clinical research have rarely impacted on patient care as quickly or as significantly as the use of oral tretinoin for the treatment of patients with APL.[17] With the use of tretinoin, tumour cells undergo maturation as patients achieve a complete response (CR), thus avoiding treatment-related complications of coagulopathy and prolonged marrow aplasia. During the past decade, its mechanism of action has been described and an appropriate dose has been determined; however, the most effective administration schedule for tretinoin, combinations with cytotoxic chemotherapy, and potential role in consolidation and/or maintenance therapy have yet to be determined.

APL is a distinct subtype of AML characterised by a specific t(15:17) balanced chromosomal translocation.[18] At the molecular level, the t(15:17) translocation results in the fusion of genes encoding the retinoic acid receptor (RAR-alpha) and the promyelocytic leukaemia (PML).[19] A hybrid PML-RAR-alpha mRNA is produced and translated into a chimeric protein, which is presumed to be involved in the pathogenesis of APL.[20]

Clinically, APL is characterised by 2 morphologically distinct forms. The more common hypergranular form of APL is usually associated with leucopenia. A more aggressive form is described as the microgranular variant (M3v) and is characterised by significant hyperleucocytosis and scantly granulated blasts with bilobed nuclei. This latter form accounts for 25 to 30% of newly diagnosed APL.[21] APL typically presents with a life-threatening coagulopathy, which usually worsens with cytotoxic therapy. In the past, with standard induction regimens the incidence of early haemorrhagic deaths was 10 to 20%.[22-24] In patients with the M3v, the risk of early haemorrhagic death is increased. Even though APL tends to be very sensitive to chemotherapy, especially the anthracyclines daunorubicin and idarubicin, the overall CR rate has not improved, primarily because of treatment-related deaths associated with the haemorrhagic diathesis.

Retinoids derived from retinol (vitamin A) are regulators of cell proliferation, differentiation and embryonal morphogenesis.[25] Interestingly, the use of the retinol derivative tretinoin was shown initially to induce CR in patients with resistant and refractory APL and, more recently, in patients with newly diagnosed APL (table II).[26-28]

These clinical results were first demonstrated in China but have since been confirmed by several other groups.[26] Moreover, both *in vitro* and *in vivo* data indicate that the induction of CR by tretinoin is associated with the differentiation of immature neoplastic promyelocytes into mature granulocytes, followed by the normal reconstitution of the bone marrow and peripheral blood counts, as the patient achieves CR.[26,27,36] In addition, tretinoin rapidly improves the underlying coagulopathy and does not induce bone marrow aplasia, thereby

reducing the incidence of fatal bleeding and sepsis in the treatment of APL. Initially, various oral doses ranging from 10 to 100 mg/m^2 of body-surface area were used; no particular dose-effect correlation was seen. Most clinical trials now use a dose of 45 mg/m^2, administered orally once daily or in 2 equally divided doses.[29-35]

Two recent randomised trials in patients with newly diagnosed APL confirmed the beneficial role of tretinoin compared with cytotoxic chemotherapy for induction of remission. Fenaux et al.[31] published results from a multicentre European trial in which 102 patients with APL were randomised to receive tretinoin followed by daunorubicin and cytarabine (ara-C) versus daunorubicin and cytarabine alone. Once CR was achieved, 2 additional cycles of chemotherapy were administered. No significant difference in the overall CR rate was observed (91% with tretinoin versus 81% with chemotherapy). There was a significant reduction in the duration of coagulopathy in the tretinoin group, and a significant improvement in disease-free survival in patients receiving tretinoin followed by chemotherapy (79 *vs* 50%, p = 0.001). In another trial, 346 patients were randomly assigned to receive either tretinoin or the combination of daunorubicin and cytarabine as induction therapy.[35] Patients who achieved CR received 2 cycles of consolidation, and those who continued to be in remission following consolidation were randomised to maintenance treatment with tretinoin or to observation. The results of this study demonstrated that tretinoin, given as either induction or maintenance therapy, resulted in an improved disease-free survival compared with cytotoxic chemotherapy alone. Tretinoin given during induction therapy did not improve the rate of CR or decrease the early mortality, but its use did reduce the likelihood of relapse. The rate of CR with tretinoin in this study (72%) was lower than the 91% rate reported in the trial published by Fenaux et al.;[31] however, in that trial most patients assigned to tretinoin also received standard chemotherapy to control hyperleucocytosis and achieve CR.[31,35]

In the early trials with tretinoin and in the trials described above, hyperleucocytosis accompanied by a 'tretinoin syndrome' (characterised by fevers, respiratory distress, radiographic infiltrates, pleural effusions, and weight gain) was seen in 10 to 25% of patients.[37] Clinical manifestations of the leucocytosis and the syndrome were prevented by treatment with full doses of chemotherapy and, in some cases, use of dexamethasone.

Between 20 and 75% of patients treated with tretinoin may require chemotherapy during induction therapy (table II). In a pilot trial, 25 of 26 patients achieved CR with tretinoin; however, 11 of these patients required the addition of 3 days of daunorubicin and 7 days of cytarabine ('3 + 7' course) when hyperleucocytosis emerged to prevent leucostasis.[30] In a randomised trial in which 54 patients were allocated to the tretinoin group, 49 (91%) achieved CR.[31] However, only 14 (26%) patients achieved CR with tretinoin alone; 35 (65% of the total) required tretinoin plus daunorubicin and cytarabine. Kanamaru et al.[32] reported on a multicentre trial where 109 patients with newly diagnosed APL were treated with tretinoin. If patients had leucocyte counts $>3 \times 10^9$/L or if the peripheral counts began to rise on tretinoin treatment, daunorubicin and cytarabine were added. Overall, 97 (89%) achieved a CR; however, 72 (66% of the total) required the addition of chemotherapy to achieve a response.

The results of these trials suggest that the combination of tretinoin and chemotherapy improves the overall prognosis of this disease. Even before the use of oral tretinoin, significant sensitivity of APL to anthracycline drugs had already been established. This sensitivity has been confirmed by a retrospective analysis of the Southwest Oncology Group, which demonstrated that increased doses of daunorubicin led to improved disease-free survival.[38] To improve the 'quality' of the CR, 20 consecutive patients with newly diagnosed APL were treated by Avvisati et al.[33] with tretinoin and idarubicin. After a median of 36 days, 18 of 20 patients achieved CR; the remaining 2 died on days 12 and 34 from myocardial infarction and

from haemoptysis, respectively. The tretinoin syndrome was observed in only 2 patients, both of whom recovered with appropriate treatment. Mandelli et al.[34] recently reported on 274 patients receiving this combination regimen of tretinoin and idarubicin. At the time of analysis, 240 of the 253 patients were evaluable. Of these, 229 (95%) had achieved a haematological response and 11 (5%) had died of early complications. Of the 240 evaluable patients, only 6 (2.5%) had developed the tretinoin syndrome.

It is now clear that, in patients with newly diagnosed APL, tretinoin appears to be the single most effective agent. However, when it is used alone, there appears to be a relatively high risk of hyperleucocytosis and occurrence of the tretinoin syndrome as well as a significant relapse rate. Therefore, patients should receive tretinoin for induction therapy concurrently with chemotherapy, specifically an anthracycline, either with the administration of tretinoin or as soon as the white blood cell count begins to increase. Consolidation chemotherapy with an anthracycline appears to decrease the overall relapse rate. Whether cytarabine adds any additional benefit to an anthracycline alone needs further evaluation. The role for tretinoin as maintenance therapy needs further investigation, especially since acquired resistance to tretinoin appears to occur. Continuous daily treatment with tretinoin is associated with a marked decrease in plasma drug concentrations.

2.2 Treatment of the Elderly Patient with AML

Another area of recent investigation into the use of oral chemotherapy agents in AML is for elderly patients who may not be candidates for intensive intravenous regimens. A regimen combining oral idarubicin 30 mg/m^2 and oral etoposide 80 mg/m^2 for 3 consecutive days for 1 to 4 cycles was recently evaluated in 28 elderly patients considered unsuitable for standard intensive induction treatments.[39] CR was achieved in 36% of patients, with a median survival of 9 months in those achieving a CR. The regimen was well tolerated and associated with only minor nonhaematological toxicity. After administration of the first course in the hospital, 40% of subsequent courses were administered on a totally outpatient basis. On the basis of these data describing a well tolerated and effective oral regimen for elderly patients with AML, additional investigations were undertaken to study the pharmacokinetics of oral idarubicin in an attempt to develop a model that could enhance clinical outcome or limit toxicity.[40] A pharmacokinetic study in 9 patients demonstrated substantial interpatient variation in absorption, resulting in a wide range of observed AUCs for idarubicin and its main metabolite, idarubicinol. More importantly, the study demonstrated a good correlation between the 24-hour trough concentration and AUC. Thus, the 24-hour trough concentration could serve as a quick and easy estimate of individual patient absorption and potentially serve as a monitoring parameter to individualise therapy. Other agents being evaluated in the elderly AML population include new oral formulations of cytarabine and combinations of subcutaneous cytarabine with oral thioguanine that can be safely administered in the outpatient setting.[41-43]

3. Current Status of Oral Treatment of ALL

Oral mercaptopurine, thioguanine, and methotrexate are standard agents used in the treatment of ALL, particularly in the paediatric population receiving prolonged regimens and not undergoing transplantation. Recent investigations to enhance oral therapy have focused on the issues of compliance, schedule, and comparisons with intravenous routes of administration. Because patients with ALL, including the paediatric population, require prolonged treatment with oral agents, noncompliance may have a substantial impact on outcome. Rates of noncompliance with oral medications in children with ALL vary from a reported 2 to 30%, as evidenced by no to minimal measurable mercaptopurine metabolites noted in several studies.[11,44] Another evaluation found that 33% of patients took less than 90% of their prescribed regimen, according to electronic measurements of compliance.[11,44]

In addition, these data indicate a trend towards a higher compliance rate with evening administration.[11] Lilleyman and Lennard[10] suggest that children undergoing ALL maintenance treatment with oral mercaptopurine and methotrexate may be best served by regular measurement of antimetabolite drug concentrations to monitor compliance. Such an approach would allow intervention to improve compliance and attempt to decrease late relapses.

Other investigations into oral therapy in ALL have also addressed the schedule of administration of medications, particularly oral mercaptopurine and methotrexate. A recent study evaluated the impact of morning versus evening administration of mercaptopurine and methotrexate, and the effect of coadministration of these drugs with food on relapse in children with ALL.[45] Multivariate analysis demonstrated that patients receiving these drugs on an evening administration schedule fared better, with a higher probability of event-free survival. Coadministration with food had no impact on relapse. Also, an inferior outcome was noted in patients with lower concentrations of intracellular cytotoxic metabolites, although the value of individual dose adjustment based on these concentrations remains unknown.

With respect to methotrexate, several studies have attempted to define the preferred route of administration during intensification, consolidation, and maintenance regimens for ALL. For intensification, Mahoney et al.[46] reported that intermediate dose intravenous methotrexate is superior to low dose oral methotrexate for prevention of relapse. For consolidation and maintenance, however, studies suggest that low dose oral regimens are as effective as intermediate dose intravenous regimens.[47,48]

4. Current Status of Oral Treatment of CML

Hydroxycarbamide and busulfan represent the historical treatment standards for initial therapy for CML. These regimens are rarely curative but provide good symptom and blood count control. More recently, interferon-α (IFNα), administered subcutaneously, has replaced these oral agents as first-line non-transplant therapy for most young patients or elderly patients with good performance status. Some data suggest that prolonged IFNα treatment prior to transplantation may adversely affect the outcome of allogeneic unrelated donor transplantation.[49] Thus, there may be renewed interest in the use of these oral agents for patients who are likely to have such transplants. In this respect, it is important to review data outlining the outcome following allogeneic transplantation based on pre-transplant hydroxycarbamide versus busulfan.[50] While overall response rates were similar with these 2 agents, transplant-related toxicity was significantly higher in patients receiving pre-transplant busulfan. Hydroxycarbamide is thus the preferred agent for initial control of CML in patients considered to be poor candidates for first-line interferon.

5. Current Status of Oral Treatment of CLL

The combination of chlorambucil and prednisone, both administered orally, has been the standard of care for many years when treating advanced-stage or symptomatic CLL. During the past few years, many clinicians have explored a more aggressive approach to the treatment of CLL, with use of intravenously administered purine analogues such as fludarabine or cladribine for first-line treatment or treatment of refractory disease. While comparative data suggest that purine analogues are superior or at least equal in efficacy to conventional chlorambucil and prednisone, these regimens generally require several days of short or continuous intravenous infusions. Given the indolent course of CLL and the primarily elderly population with this disease, interest in developing an oral purine analogue regimen (specifically cladribine) prompted a pharmacokinetic study to evaluate its bioavailability.[51] An absolute bioavailability of 37 to 50% was observed in pharmacokinetic studies for cladribine, with linear, predictable absorption and disposition

characteristics, suggesting the oral route of administration warranted further investigation. In previously untreated CLL patients, oral cladribine for 5 consecutive days every month resulted in CR and partial response rates of 38 and 37%, respectively, and an overall survival rate of 82% at 2 years.[52] While these response data were acceptable and at least comparable to those with other regimens, serious infectious toxicity occurred in one-third of patients. Such rates of infection may affect quality of life, particularly when this type of regimen is administered for prolonged periods of time. Given the correlation observed between cladribine AUC and the degree of neutropenia, Liliemark et al.[53] developed and evaluated a limited sampling strategy for estimation of cladribine AUC. Such strategies may eventually allow for individualisation of the cladribine dose, thus limiting treatment complications such as infections.

6. Current Status of Oral Chemotherapy in Blood and Bone Marrow Transplantation

High dose oral busulfan is a commonly used component of the transplant preparative regimens administered to patients with haematological malignancies undergoing autologous or allogeneic blood or marrow transplantation. Currently, busulfan is marketed only as an oral formulation in the US, although intravenous formulations are under development. Oral administration of high dose busulfan represents a unique dilemma, requiring an understanding of its pharmacokinetic and pharmacodynamic profiles, both of which have recently been explored extensively. After high dose administration, busulfan disposition exhibits wide intrapatient and interpatient variability due to a number of factors, including age, hepatic function, circadian variations, and drug interactions.[3,54,55]

When high fixed doses of busulfan were used, particularly in children receiving doses on an mg/kg basis, wide interpatient variability in both response and toxicity has been reported.[56,57] Investigation into this phenomenon revealed that infants and young children handle high dose busulfan differently and more unpredictably than adults receiving similar doses.[56,57] In many cases, children were exposed to less drug than adults given similar doses, because of the more rapid clearance in children. On the basis of these data, high dose busulfan in children was investigated using an mg/m^2 approach to administration, specifically, 40 mg/m^2 every 6 hours for a total of 16 doses rather than 1 mg/kg every 6 hours for 16 doses.[58] This administration strategy resulted in higher exposures to busulfan than when administered on an mg/kg basis, and also in exposures similar to those observed in adults with acceptable toxicity.[58] Another new administration strategy for high dose busulfan in children is the administration of higher single daily doses rather than 4 divided doses per day.[59] This administration strategy produced total busulfan exposures similar to those seen in adults. In the future, such an administration strategy may facilitate the delivery of high dose busulfan on an outpatient basis to selected patients.

The disposition of high dose busulfan after oral administration has also been extensively studied in adults.[54,60] In addition to observations of wide interpatient variability and, to a lesser degree, intrapatient variability, some studies in adults also suggest a correlation between toxicity [particularly hepatic veno-occlusive disease (VOD)] and increased busulfan exposure as measured by the AUC.[60-63] Decreased busulfan exposure, as measured by the AUC or steady-state concentration, has also been associated with an increased risk of graft rejection and relapse.[62,64] Such data have prompted some centres to incorporate individualised administration of high dose busulfan based on pharmacokinetic monitoring of the AUC. While the clinical benefit of such an individualised administration approach is debatable,[65,66] Grochow et al. did report a decreased incidence of VOD in patients receiving individually adjusted doses of high dose busulfan targeted to achieve a desired AUC.[67] Although monitoring of busulfan plasma concentrations is not the standard of care in all transplant centres, it does represent the potential of

such an approach when using oral chemotherapy agents.

7. Conclusion

Even though recent advances have expanded the role of oral chemotherapy agents in the treatment of leukaemia, continued investigations into how to enhance the applicability of oral therapy are warranted. To minimise the risk of relapse, further definition of the duration and schedule of tretinoin as first-line therapy for APL is also needed. Pharmacoeconomic and quality-of-life evaluations will also be essential to help further delineate the most appropriate role of oral therapy in the treatment of leukaemia.

References

1. Bustamante CI, Wade JC. Herpes simplex virus infection in the immunocompromised cancer patient. J Clin Oncol 1991; 9: 1903-15
2. Ptachcinski RJ, Burckart GJ, Venkataramanan R. Cyclosporine. Drug Intell Clin Pharm 1985; 19: 90-100
3. DeMario MD, Ratain MJ. Oral chemotherapy: rationale and future directions. J Clin Oncol 1998; 16: 2557-67
4. Hande KR, Krozely MG, Greco FA, et al. Bioavailability of low-dose oral etoposide. J Clin Oncol 1993; 11: 374-7
5. Smyth RD, Pfeffer M, Scalzo A, et al. Bioavailability and pharmacokinetics of etoposide (VP-16). Semin Oncol 1985; 12 Suppl. 2: 48-51
6. Herbert MF, Roberts JP, Prueksaritanost T, et al. Bioavailability of cyclosporine with concomitant rifampin administration is markedly less than predicted by hepatic enzyme induction. Clin Pharmacol Ther 1992; 52: 453-7
7. Osowski CL, Dix SP, Lin LS, et al. Evaluation of the drug interaction between intravenous high-dose fluconazole and cyclosporine or tacrolimus in bone marrow transplant patients. Transplantation 1996; 61: 1268-72
8. Kobayashi K, Ratain MJ, Fleming GF, et al. A phase I study of CYP3A4 modulation of oral etoposide with ketoconazole in patients with advanced cancer. Proc Am Soc Clin Oncol 1996; 15: 471a
9. Lee CR, Nicholson PW, Souhami RL, et al. Patient compliance with prolonged low-dose oral etoposide for small cell lung cancer. Br J Cancer 1993; 67: 630-4
10. Lilleyman JS, Lennard L. Non-compliance with oral chemotherapy in childhood leukaemia. BMJ 1996; 313: 1219-20
11. Lau RC, Matsui D, Greenberg M, et al. Electronic measurement of compliance with mercaptopurine in pediatric patients with acute lymphoblastic leukemia. Med Pediatr Oncol 1998; 30: 85-90
12. Lee CR, Nicholson PW, Souhami RL, et al. Patient compliance with oral chemotherapy as assessed by a novel oral technique. J Clin Oncol 1992; 10: 1007-13
13. Lee C, Nicholson P, Souhami R, et al. Patient compliance with prolonged low-dose oral etoposide for small cell lung cancer. Br J Cancer 1993; 67: 630-4
14. Levine AM, Richardson JL, Marks G, et al. Compliance with oral drug therapy in patients with hematologic malignancy. J Clin Oncol 1987; 5: 1469-76
15. Sullivan SD, Mozaffari E, Johnson ES, et al. An economic evaluation of oral compared with intravenous ganciclovir for maintenance treatment of newly diagnosed cytomegalovirus retinitis in AIDS patients. Clin Ther 1996; 18: 546-58
16. Liu G, Franssen E, Fitch M, et al. Patient preference for oral versus intravenous palliative chemotherapy. J Clin Oncol 1997; 15: 110-5
17. Warrell RP, de-The H, Wang ZY, et al. Acute promyelocytic leukemia. N Engl J Med 1993; 329: 177-89
18. Rowley JD, Golomb HM, Dougherty C. 15/17 Translocation: a consistent chromosomal change in acute promyelocytic leukaemia. Lancet 1977; 1: 549-50
19. DeThe J, Chomienne C, Lanotte M, et al. The t(15;17) translocation of acute promyelocytic leukaemia fuses the retinoic acid receptor alpha gene to a novel transcribed locus. Nature 1990; 347: 558-61
20. DeThe H, Lavau C, Marchio A, et al. The PML-RAR alpha fusion mRNA generated by the t(15;17) translocation in acute promyelocytic leukemia encodes a functionally altered RAR. Cell 1991; 66: 675-84
21. Stone RM, Mayer RJ. The unique aspects of acute promyelocytic leukemia. J Clin Oncol 1990; 8: 1913-21
22. Kantarjian HM, Keating MJ, Walters RS, et al. Acute promyelocytic leukemia: M.D. Anderson Hospital experience. Am J Med 1986; 80: 789-97
23. Sanz MA, Jarque I, Martin G, et al. Acute promyelocytic leukemia: therapy results and prognostic factors. Cancer 1988; 61: 7-13
24. Gralnick HR, Sultan C. Acute promyelocytic leukaemia: haemorrhagic manifestation and morphologic criteria. Br J Haematol 1975; 29: 373-6
25. Tabin CJ. Retinoids, homeoboxes, and growth factors: toward molecular models for limb development. Cell 1991; 66: 199-217
26. Sun GL, Huang YG, Chang XF, et al. Clinical study on all-trans retinoic acid in treatment of 544 cases of acute promyelocytic leukemia. Chin J Hematol 1992; 13: 135-7
27. Castaigne S, Chomienne C, Daniel MT, et al. All-trans retinoic acid as a differentiation therapy for acute promyelocytic leukemia. I. Clinical results. Blood 1990; 76: 1704-9
28. Warrell Jr RP, Frankel SR, Miller Jr WH, et al. Differentiation therapy of acute promyelocytic leukemia with tretinoin (all-trans-retinoic acid). N Engl J Med 1991; 324: 1385-93
29. Huang ME, Ye YC, Chen SR, et al. Use of all-trans retinoic acid in the treatment of acute promyelocytic leukemia. Blood 1988; 72: 567-72
30. Fenaux P, Castaigne S, Dombret H, et al. All-trans retinoic acid following by intensive chemotherapy gives a high complete remission rate and may prolong remissions in newly diagnosed acute promyelocytic leukemia: a pilot study on 26 cases. Blood 1992; 80: 2176-81
31. Fenaux P, Le Deley MC, Castaigne S, et al. Effect of all-trans retinoic acid in newly diagnosed acute promyelocytic leukemia: results of a multi-center randomized trial: European APL 91 Group. Blood 1993; 82: 3241-9
32. Kanamaru A, Takemoto Y, Tanimoto M, et al. All-trans retinoic acid for the treatment of newly diagnosed acute promyelocytic leukemia. Blood 1995; 85: 1202-6
33. Avvisati G, Lo Cocco F, Diverio D, et al. AIDA (all-trans retinoic acid + idarubicin) in newly diagnosed acute promyelocytic leukemia: a Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) pilot study. Blood 1996; 88: 1390-8
34. Mandelli F, Diverio D, Avvisati G, et al. Molecular remission in PML/RAR alpha-positive acute promyelocytic leukemia by combined all-trans retinoic acid and idarubicin (AIDA) therapy. Gruppo Italiano-Malattie Ematologiche Maligne dell'Adulto and Associazione Italiana di Ematologia ed

Oncologia Pediatrica Cooperative Groups. Blood 1997; 90: 1014-21
35. Tallman MS, Anderson JW, Schiffer CA, et al. All-trans retinoic acid in acute myelocytic leukemia. N Engl J Med 1997; 337: 1021-8
36. Chen ZX, Xue YQ, Zhang RI, et al. A clinical and experimental study on all-trans retinoic acid-treated acute promyelocytic leukemia patients. Blood 1991; 78: 1413-9
37. Frankel SR, Eardley A, Lauwers G, et al. The 'retinoic acid syndrome' in acute promyelocytic leukemia. Ann Intern Med 1992; 117: 292-6
38. Head D, Kopecky KJ, Weick J, et al. Effect of aggressive daunomycin therapy on survival in acute promyelocytic leukemia without cytarabine. J Clin Oncol 1997; 15: 483-90
39. Jackson GH, Taylor PR, Iqbal A, et al. The use of an all oral chemotherapy (idarubicin and etoposide) in the treatment of acute myeloid leukemia in the elderly: a report of toxicity and efficacy. Leukemia 1997; 11: 1193-6
40. Schleyer E, Kuhn S, Ruhrs H, et al. Oral idarubicin pharmacokinetics – correlation of trough level with idarubicin area under curve. Leukemia 1997; 11 Suppl. 5: S15-21
41. Schwendener RA, Horber DH, Odermatt B, et al. Oral antitumor activity in murine L1210 leukemia and pharmacological properties of liposome formulations of N4-alkyl derivatives of 1-beta-D-arabinofuranosylcytosine. J Cancer Res Clin Oncol 1996; 122: 102-8
42. Okumura H, Yoshida T, Takamatsu H, et al. Treatment of acute myeloid leukemia and myelodysplastic syndrome with orally administered cytarabine ocfosfate and granulocyte colony-stimulating factor. Int J Hematol 1997; 65: 263-8
43. Munshi NC, Tricot GJ. Single weekly cytosine arabinoside and oral 6-thioguanine in patients with myelodysplastic syndrome and acute myeloid leukemia. Ann Hematol 1997; 74: 111-5
44. Lancaster D, Lennard L, Lilleyman JS. Profile of non-compliance in lymphoblastic leukemia. Arch Dis Child 1997; 76: 365-6
45. Schmiegelow K, Glomstein A, Kristinsson J, et al. Impact of morning versus evening schedule for oral methotrexate and 6-mercaptopurine on relapse risk for children with acute lymphoblastic leukemia. Nordic Society for Pediatric Hematology and Oncology (NOPHO). J Pediatr Hematol Oncol 1997; 19: 102-9
46. Mahoney Jr DH, Shuster J, Nitschke R, et al. Intermediate-dose intravenous methotrexate with intravenous mercaptopurine is superior to repetitive low-dose oral methotrexate with intravenous mercaptopurine for children with lower-risk B-lineage acute lymphoblastic leukemia: a Pediatric Oncology Group phase III trial. J Clin Oncol 1998; 16: 246-54
47. Lange BJ, Blatt J, Sather HN, et al. Randomized comparison of moderate-dose methotrexate infusions to oral methotrexate in children with intermediate risk acute lymphoblastic leukemia: a Children's Cancer Group study. Med Pediatr Oncol 1996; 27: 15-20
48. Winick N, Shuster JJ, Bowman WP, et al. Intensive oral methotrexate protects against lymphoid marrow relapse in childhood B-precursor acute lymphoblastic leukemia. J Clin Oncol 1996; 14: 2803-11
49. Morton AJ, Gooley T, Hansen JA, et al. Impact of pre-transplant interferon-alpha on outcome of unrelated donor marrow transplants for chronic myeloid leukemia (CML) in first chronic phase. Blood 1997; 90 Suppl. 1: 123a
50. Kantarjian HM, O'Brien S, Anderline P, et al. Treatment of chronic myelogenous leukemia: current status and investigational options. Blood 1996; 87: 3069-81
51. Saven A, Cheung WK, Smith I, et al. Pharmacokinetic study of oral and bolus intravenous 2-chlorodeoxyadenosine in patients with malignancy. J Clin Oncol 1996; 14: 978-83
52. Juliusson G, Christiansen I, Hansen MM, et al. Oral cladribine as primary therapy for patients with B-cell chronic lymphocytic leukemia. J Clin Oncol 1996; 14: 2160-6
53. Liliemark J, Albertioni F, Juliusson G, et al. A limited sampling strategy for estimation of the cladribine plasma area under the concentration versus time curve after intermittent i.v. infusion, s.c. injection, and oral administration. Cancer Chemother Pharmacol 1996; 38: 536-40
54. Hassan M, Oberg G, Bekassy AN, et al. Pharmacokinetics of high-dose busulfan in relation to age and chronopharmacology. Cancer Chemother Pharmacol 1991; 28: 130-4
55. Vassal G. Pharmacologically-guided dose adjustment of busulfan in high-dose chemotherapy regimens: rationale and pitfalls. Anticancer Res 1994; 14: 2363-70
56. Vassal G, Gouyette A, Hartmann O, et al. Pharmacokinetics of high-dose busulfan in children. Cancer Chemother Pharmacol 1989; 24: 386-90
57. Grochow LB, Krivit W, Whitley CB, et al. Busulfan disposition in children. Blood 1990; 75: 1723-7
58. Yeager AM, Wagner Jr JE, Graham ML, et al. Optimization of busulfan dosage in children undergoing bone marrow transplantation: a pharmacokinetic study of dose escalation. Blood 1992; 80: 2425-8
59. Shaw PJ, Scharing CE, Brian RJ, et al. Busulfan pharmacokinetics using a single daily high-dose regimen in children with acute leukemia. Blood 1994; 84: 2357-62
60. Grochow LB, Jones RJ, Brundrett RB, et al. Pharmacokinetics of busulfan: correlation with veno-occlusive disease in patients undergoing bone marrow transplantation. Cancer Chemother Pharmacol 1989; 25: 55-61
61. Dix SP, Wingard JR, Mullins RE, et al. Association of busulfan area under the curve with veno-occlusive disease following BMT. Bone Marrow Transplant 1996; 17: 225-30
62. Slattery JT, Sanders JE, Buckner CD, et al. Graft-rejections and toxicity following bone marrow transplantation in relation to busulfan pharmacokinetics. Bone Marrow Transplant 1995; 16: 31-42
63. Ljungman P, Hassan M, Bekassy AN, et al. High busulfan concentrations are associated with increased transplant-related mortality in allogeneic bone marrow transplant patients. Bone Marrow Transplant 1997; 20: 909-13
64. Slattery JT, Clift RA, Buckner CD, et al. Marrow transplantation for chronic myeloid leukemia: the influence of plasma busulfan levels on the outcome of transplantation. Blood 1997; 89: 3055-60
65. Schuler U, Schroer S, Kuhnle A, et al. Busulfan pharmacokinetics in bone marrow transplant patients: is drug monitoring warranted? Bone Marrow Transplant 1994; 14: 759-65
66. Pawlowska AB, Blazar BR, Angelucci E, et al. Relationship of plasma pharmacokinetics of high-dose oral busulfan to the outcome of allogeneic bone marrow transplantation in children with thalassemia. Bone Marrow Transplant 1997; 20: 915-20
67. Grochow LB. Busulfan disposition: the role of therapeutic monitoring in bone marrow transplantation induction regimens. Semin Oncol 1993; 20 Suppl. 4: 18-25

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