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Oral Cancer Chemotherapy in Paediatric Patients

Obstacles and Potential for Development and Utilisation

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Abstract

Although most cancer chemotherapy in children is administered parenterally, oral formulations are becoming increasingly available for use in patients as young as infants. Incentives for this approach include safety, flexibility, reduced financial cost, improved quality of life, and the potential for improved efficacy. The ability to deliver chemotherapy at home and apply schedules of administration that increase the agent's efficacy because patients do not require hospitalisation or visits to the clinic renders oral chemotherapy particularly attractive. Obstacles to oral chemotherapy in paediatric patients include restrictions in dose size and schedule, uncertain or low bioavailability, adverse effects of malabsorption, and adherence (noncompliance and refusal to take oral chemotherapy). Techniques to overcome most of these limitations are available or can be developed, and lack of an oral formulation can be solved in many instances by the pharmaceutical industry. Future developments in oral chemotherapy should not be limited to adult patient applications.

Remarkably little chemotherapy is administered orally to children with cancer. In children with solid tumours, for example, only those with brain tumours are given oral therapy with any significant frequency. In actuality, most of these patients receive only parenteral therapy. The oral therapy used in children with leukaemia and lymphoma, such as acute lymphoblastic leukaemia (ALL), essentially consists of only antimetabolites and corticosteroids. In patients with acute progranulocytic leukaemia, tretinoin (all-*trans* retinoic acid) is given orally, but the rest of the therapy is parenteral. Despite these common practices, there is a potential for the increased use of oral chemotherapy in children with cancer. As more oral agents such as etoposide phosphate and vinorelbine are developed, this potential will increase. The continued decline in healthcare funding provides a further incentive for the use of orally administered agents.

Oral chemotherapy is being used increasingly in our Child and Adolescent Center at the University of Texas M.D. Anderson Cancer Center. For example, the most widely used regimen for children with relapsed gliomas is now a combination of all orally administered agents: thioguanine, procarbazine, lomustine (CCNU), and hydroxycarbamide (hydroxyurea) [TPCH; fig. 1]. Oral temozolomide has gained popularity for the treatment of refractory brain tumours in children. For example, the Children's Cancer Group Phase II Study of oral temozolomide accrued 105 patients in less than 14 months (M. Krailo, personal communication). Our planned trials include oral topotecan and the

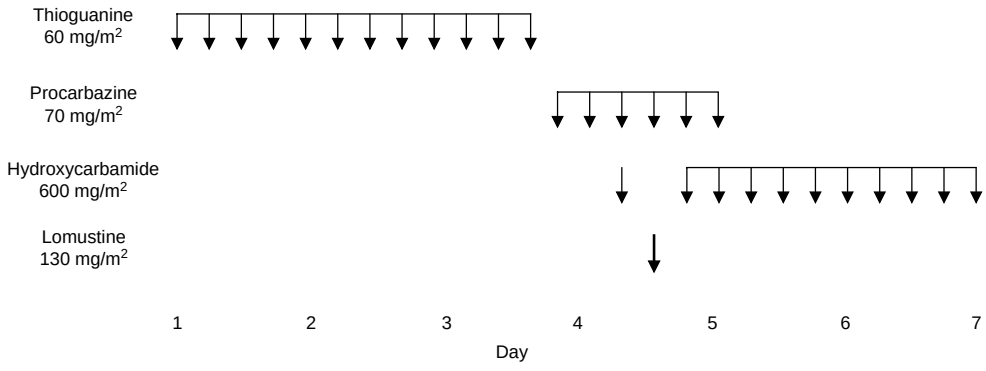

Fig. 1. An all-oral regimen of thioguanine, procarbazine, lomustine (CCNU), and hydroxycarbamide (hydroxyurea) for glioma therapy.

combination of temozolomide with lomustine in another all-oral regimen. In addition, a regimen of daily oral etoposide is now used extensively for the palliative treatment of a variety of solid tumours. Etoposide is also being used orally as a radiosensitiser in children with brain tumours undergoing radiotherapy. Furthermore, an all-parenteral regimen used at our center during the early 1990s for the treatment of ALL has now been replaced by an all-outpatient regimen.

Examples of non-chemotherapy oral applications in children at our institution include treatment of patients at a low risk of severe complications from fever and neutropenia. We are treating these patients with oral antibiotics (ciprofloxacin, trovafloxacin) at home or in lodging near the hospital, provided that they can be evaluated daily in our outpatient department. The treatment of varicella zoster infection has been converted from intravenous aciclovir to oral valaciclovir, a prodrug of aciclovir that has improved oral bioavailability. Oral odansetron for the prevention of nausea and vomiting has been particularly effective, and now there is a rapidly disintegrating tablet version that need not be swallowed. When it is held in the mouth, the agent dissolves in less than a minute. For analgesia prior to bone marrow and lumbar punctures, we are studying administration of fentanyl via oralets (lollipop-like vehicles for absorption from the oral cavity). As a direct result of these changes, hospitalisation rates have been reduced, our patients are more mobile, and they are able to spend more time at home or in their lodgings, much to their satisfaction and that of their families and their payers.

Given the current trend towards the use of oral chemotherapy, this review summarises the rationale for parenteral chemotherapy in paediatric patients with cancer, the obstacles to the use of oral chemotherapy, and the potential benefits to be gained from overcoming the obstacles. Finally, this paper concludes with a request to the pharmaceutical industry to continue the development of oral formulations of antineoplastic agents suitable for paediatric patients.

1. Background and Rationale for Parenteral Chemotherapy

For most of the cancer chemotherapeutic agents used to treat cancer in children, there is no oral formulation, and there is simply no choice but the parenteral route of administration. There has also been a natural bias against the use of oral chemotherapy in children with cancer. One factor that has discouraged the development of oral agents is the popularity of high dose chemotherapy, regardless of whether or not the high dose parenteral therapy has been shown to be more effective than oral therapy.

Even when an oral formulation is available, paediatric cancer patients are nonetheless given the parenteral form of the agent. One of the most frequently cited reasons for this is that it is 'the only way to know that the drug makes it into the patient'. This is understandable given the fact that there is a significant probability of long term disease control in most children with cancer, which hinges on the effectiveness of the therapy. Therefore, paediatric oncologists have traditionally been reluctant to do anything that might risk treatment failure. This includes the possible risk that some of the drug does not 'make it into the patient' because either it is not absorbed from the gastrointestinal tract or it does not reach the sites of absorption as a result of vomiting or noncompliance. With the widespread availability of indwelling venous access devices, it is easier to deliver the drug intravenously than to have the child swallow it and ensure that it has been administered.

Another factor that has influenced the choice of route of administration is the high success rate achieved with current parenteral therapy. This has led to the proverbial 'if it ain't broke, don't fix it' attitude. The results are undeniable. As predicted from US Surveillance, Epidemiology, and End-Results (SEER) data, national cure rates are predicted to exceed 80% in children with cancer who are less than 15 years of age.[1]

2. Advantages of Oral Chemotherapy

Despite the bias against the administration of oral therapy and other obstacles reviewed below, oral chemotherapy in paediatric patients has distinct advantages that should be considered when weighing up the overall relative merits of parenteral and enteral therapy.

2.1 Equivalent Efficacy of Oral and Parenteral Administration

Oral versus parenteral antimetabolite therapy of the most common childhood cancer, ALL, is a case in point. Regardless of the putative advantages of parenteral administration, there is remarkably little evidence that it is associated with a survival or disease-control advantage. On the contrary, trials comparing oral and parenteral administration of comparable doses of agents have failed to show an advantage with parenteral administration. In particular, randomised trials of intramuscular versus oral methotrexate in the treatment of childhood lymphoblastic leukaemia, the setting in which most of these trials have been conducted, have yielded equivalent disease-free and overall survival rates.[2]

Oral methotrexate therapy has been compared with intravenous methotrexate therapy, the latter given at higher doses than can be absorbed by the oral route. Only one prospective controlled trial showed better results in patients given the higher dose intravenous therapy. This trial was conducted by the Pediatric Oncology Group in children with lower risk B-lineage ALL.[3] After induction of remission, patients were randomised to receive an intensive course of therapy consisting of either intermediate dose intravenous methotrexate (1000 mg/m^2) and intravenous mercaptopurine or repeated administration of oral methotrexate (30 mg/m^2 every 6 hours for 6 doses) and intravenous mercaptopurine. 12 courses of the 2 agents were administered at 2-week intervals. The 4-year continuous complete remission rate was 80.3% [standard error (SE) = 2.9%] in 349 patients who were randomised to receive methotrexate intravenously, and 75.9% (SE = 3.1%) in 350 patients randomised to receive methotrexate orally. Although the difference was statistically significant ($p = 0.013$) in favour of the intravenous regimen, the absolute difference in the event rate was only 4.4%. This means that fewer than 1 in 20 patients benefited from the higher intravenous dose, and that the additional therapy was not beneficial in the other 19. This is particularly concerning because there was a statistically significant greater incidence of toxicities associated with higher dose intravenous methotrexate therapy. These toxicities, which included neutropenia, thrombocytopenia, bacterial sepsis, neurotoxicity, and stomatitis, necessitated more hospitalisations. It remains to be determined whether the modest prolongation of

continuous complete remission associated with intravenous therapy will be maintained over time and whether overall survival will ultimately be better than with oral therapy. Other randomised studies either have not shown an advantage with high dose methotrexate therapy[4] or have included changes in therapy other than the route of administration and dose of methotrexate, thus obscuring the results.[5]

2.2 Lack of Correlation between Systemic Drug Concentrations and Outcome

If intravenously administered therapy ultimately proves to be superior to oral administration, this could be due in part to decreased variations in the plasma concentrations of agents when given by the parenteral route. It is therefore important to determine whether the plasma concentration-time profile of an agent correlates with outcome. The study by Balis et al. noted earlier has already shed light on this by showing that there was no consistent correlation between outcome and the area under the plasma concentration-time curve (AUC) for either mercaptopurine or methotrexate, or between outcome and erythrocyte thioguanine nucleotide concentrations (fig. 2).[6] These investigators concluded that the current practice of increasing or decreasing the dose of methotrexate and mercaptopurine on the basis of the patient's haematological and hepatic toxicities is more rational than measuring drug concentrations in the patient's blood and attempting to use therapeutic drug monitoring to guide therapy.

2.3 Increased Safety

Indwelling devices for access to the venous system are not necessary in patients receiving oral chemotherapy. As a result, there are no attendant risks of infection or thrombosis. The risk of extravasation necrosis is also nonexistent. Toxicities associated with the vehicles used for the aqueous dissolution of agents to be administered intravenously are avoided as well. A further advantage of the oral administration of agents is that gastrointestinal adverse effects can serve as a safeguard against inadvertent overdoses.

2.4 Increased Flexibility and Potential for Improved Efficacy

Oral therapy may allow greater flexibility in dosage than is possible with intravenous therapy. For example, drugs that require daily administration are easier to give orally than intravenously

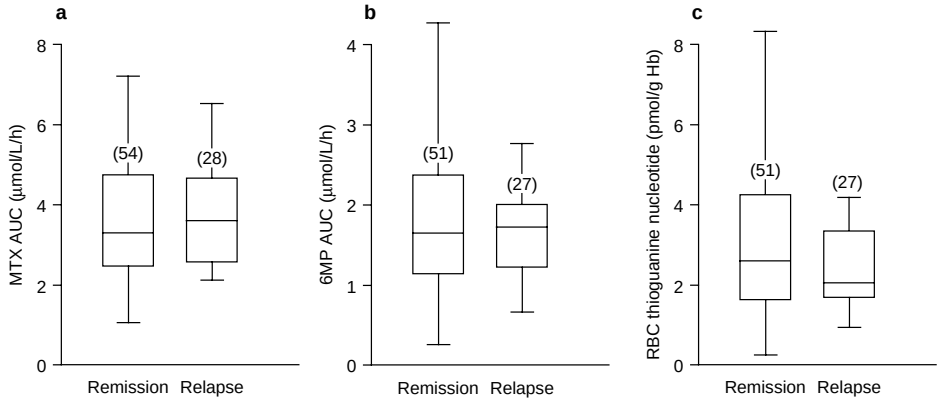

Fig. 2. Box plots of the area under the plasma concentration-time curve (AUC) for (**a**) methotrexate (MTX) and (**b**) mercaptopurine (MP) and (**c**) the erythrocyte (RBC) thioguanine nucleotide concentrations versus outcome in 89 children with acute lymphoblastic leukaemia. Numbers in parentheses represent the numbers of patients who remained in remission or who subsequently relapsed. In each panel, the boxes enclose the first and third quartiles (the middle 50% of the data); the horizontal line within each box is the median value; and the bars denote the range (reprinted from Balis et al.[6] with permission).

if an oral preparation is available. Unusual and irregular dosage schedules, such as alternate-day or Monday-Wednesday-Friday administration, also lend themselves to oral administration. The oral administration of etoposide shortly before each daily radiotherapy session is much more manageable with oral therapy. Continuous low dose exposure, such as that achieved by continuous intravenous infusions, and diurnal patterns can be mimicked by oral regimens. This flexibility may in fact improve the efficacy of therapy over that achieved by parenteral regimens. One example of how the flexibility of oral chemotherapy may be advantageous is the benefit of evening as opposed to morning administration of mercaptopurine and methotrexate in the treatment of ALL.[7] Daily evening administration is more readily accomplished with oral than parenteral therapy.

2.5 Improved Quality of Life

The most compelling reason for giving oral chemotherapy is the improved quality of life for both patients and their families. Being able to receive chemotherapy in the comfort of the home and surrounded by family is obviously better than receiving the same treatment at a healthcare institution. This was documented by Close and colleagues[8] at the Children's Hospital of Philadelphia, who prospectively evaluated a course of chemotherapy administered at home after 2 courses of the same chemotherapy administered in the hospital. Four types of regimens were evaluated in 14 patients: (i) ifosfamide, etoposide, and vincristine; (ii) cisplatin, lomustine, and vincristine; (iii) high dose cyclophosphamide; and (iv) high dose methotrexate with folinic acid (leucovorin) rescue. Although all chemotherapy was given intravenously, this study showed that, in particular, the quality of life of patients receiving chemotherapy at home was quantitatively and statistically superior from the standpoint of nearly every parameter measured. For the patient, this included a sense of well-being and independence, a good appetite, the ability to do school work, and improved mood. For the parents, this included being able to keep up with household tasks and work responsibilities, and to spend time with their spouse and other children in the family.

Another quality-of-life–related advantage with oral chemotherapy is that it eliminates the need to insert percutaneous needles for the intravenous administration of agents or for repeated entry into a subcutaneous port connected to vascular catheters, and thus avoids the associated pain. The relative ease of administration of oral over parenteral administration is obvious. Most children prefer to take medication by mouth, especially when the alternative is an injection or visit to the clinic or hospital. For this reason, pre-anaesthetic medication for children undergoing surgery is often given orally rather than intramuscularly.[9]

Oral chemotherapy is a particularly desirable alternative for palliative care in the child whose cancer is not curable. The time remaining for such children should be as pleasant as possible. Being able to spend that time at home with family, relatives, and friends is one of the most important objectives. Oral chemotherapy makes this more possible than therapy given by any other route.

2.6 Reduced Financial Cost

The frequency of hospital, physician, pharmacist and nurse encounters, and the associated costs can be dramatically reduced through the oral administration of chemotherapy. In fact, the overall cost of care can be reduced by therapy given at home. This was shown in the previously cited study conducted by Close et al.,[8] in which the courses of intravenous chemotherapy administered at home proved to be statistically less expensive in terms of the medical costs, out-of-pocket expenses, and loss of income. The cost of oral chemotherapy given at home would be less, because the cost of the programmable pumps to deliver the chemotherapy and the attendant costs would also be eliminated.

3. Specific Obstacles to Oral Chemotherapy in Paediatric Cancer Patients

Specific obstacles to the use of oral chemotherapy in children with cancer are both similar to and different from those present in adult patients. A summary of these obstacles follows, with an emphasis on the differences.

3.1 Dose Restrictions

The desired dose in a child may be less than the smallest available solid formulation because the initially developed and often the only formulations are developed for adults. Although most tablets are scored, the requisite dose may still be less than in half the tablet. In these situations the tablet has to be fractionated or the capsule opened and the contents divided, which may result in substantial inaccuracies and may also not be feasible. One solution is to administer a whole tablet or capsule in lieu of the number of smaller doses that together equal the dose in a tablet or capsule. For example, a dose of one-third of a tablet daily may be prescribed as one tablet every 3 days. The effectiveness of the agent may be compromised, however, because of the longer intervals between doses. There may also be a greater risk of toxicity because of the higher peak concentrations that would occur. The oral administration of some solid formulations in children may also be impractical.

A further difficulty is that rounding off a dose to the nearest tablet or capsule size may lead to dose inaccuracies, with variations that are potentially less effective or more toxic in children than in adults. For example, to achieve daily doses of mercaptopurine in the 32 to 42mg range, doses of 25mg (half a tablet) and 50mg (1 tablet) may be given alternately on successive days, with a resulting average daily dose of 37.5mg. Similarly, to achieve doses in the 57 to 67mg range, doses of 50mg (1 tablet) and 100mg (1.5 tablets) may be given alternately on successive days. However, the resulting day-to-day variation in the systemic concentration of the agent could make the difference between toxicity and efficacy. This is further complicated by the fact that there are no data on whether or how these schedules alter the toxicity or efficacy of most of the agents that can be given in this way. Such fractionated schedules are also frequently complicated.

The use of liquid formulations would generally circumvent these administration problems, but not all agents come in liquid preparations. In addition, it is difficult to accurately measure and administer very small doses of a liquid medication.

3.2 Administration Constraints

The chemotherapy used in children differs substantially from that used in adults because of the physical and psychological limitations inherent in children. Specifically, young children often cannot swallow capsules or tablets or have difficulty doing so. In this event, tablets can be crushed or capsules opened and the contents suspended in a liquid or semisolid vehicle so they can be ingested. If a liquid formulation is available, the desired amount can be measured and administered using a device that ensures the child swallows the dose intended. Syringes and a variety of measuring spoons, cups, and tubes are often used for this purpose.

The taste of the agent or the vehicle may further hinder ingestion of medication by a child, and may also lead to adverse interactions between the patient and the parent responsible for giving the medication at a time when a close and trusting parent-child relationship is particularly desirable. One way to circumvent the psychological stress and struggles associated with this problem may be to have a responsible guardian other than a parent or close family member administer the agent. Giving the agent according to a prescribed schedule is a further challenge for most families with children receiving oral chemotherapy, in terms of both preparing each dose and of remembering to do so.

Concurrent nausea, vomiting, mucositis, abdominal distress, and other gastrointestinal problems may also prevent the oral ingestion of cancer chemotherapy agents. In addition, the agent may

be vomited after ingestion. This may lead to uncertainty as to how much drug was retained, whether the dose should be repeated, and, if so, how much should be dispensed.

3.3 Bioavailability and Malabsorption

Unpredictable and limited bioavailability and malabsorption of orally administered agents may be other barriers to effective oral chemotherapy in children. For example, the oral bioavailability of vinorelbine is much more variable in children than in adults. Under controlled circumstances, a range of 6 to 130% was observed in 12 children compared with a narrower range in adults.[10]

As another example, the plasma concentrations of methotrexate and mercaptopurine, the most widely used oral agents for leukaemia therapy, vary markedly among paediatric patients. This was observed in the Children's Cancer Group CCG-105PH study, in which Balis and associates[6] measured the AUC in 89 children with intermediate-risk ALL. All patients were treated with a standard regimen. The maintenance phase consisted of weekly oral administration of methotrexate and daily oral administration of mercaptopurine at starting doses of 20 mg/m^2 and 75 mg/m^2, respectively. An erythrocyte sample was obtained before the first doses of methotrexate and mercaptopurine and on multiple maintenance cycles. Plasma samples were obtained frequently during the 8 hours after the simultaneous administration of methotrexate and mercaptopurine. Subsequent changes in the doses of either agent from those in the primary treatment protocol were made to maintain the neutrophil count between 1×10^3 and 2×10^3 cells/μl and the platelet count above 1×10^5 cells/μl. Over the 191 methotrexate doses and 190 mercaptopurine doses that were monitored, the AUC of methotrexate was highly variable, ranging from 0.11 to 8 μmol/L/h, while the AUC of mercaptopurine ranged from 0.63 to 12 μmol/L/h. The erythrocyte thioguanine nucleotide concentrations were similarly variable, ranging from 0 to 10 pmol/g haemoglobin.

Even if the limitations in bioavailability are overcome at the start of therapy by monitoring the drug blood concentrations and adjusting the doses in accordance with these or with end-organ effects, absorption can still be unpredictable in individual patients because of intrapatient variability. Enterally delivered drugs may also be locally toxic to the intestinal mucosa and thereby impair their own absorption.

3.4 Compliance

According to a recent review by Davies, Lilleyman, and Lennard,[11,12] 10 to 30% of children with cancer do not take, or are not given, a substantial amount of their prescribed oral chemotherapy. In the most recently reported study in which a pill container with an electronic tracking device was used, 8 of 24 patients who were aged 3 to 17 years took less than 90% of the prescribed mercaptopurine, and 4 took less than 80%.[13] Other investigators have observed no trace of mercaptopurine in the urine of paediatric patients the morning after a scheduled evening dose.[14] Compliance may be particularly problematical in adolescent patients. In separate studies, 2 groups of investigators noted noncompliance rates as high as 50% in patients in this age group.[15-17] An age dependence was not observed, however, in the most recent report that was based on accurate electronic tracking.[13]

4. Conclusions

There are many circumstances in which oral therapy is not feasible. Despite this, there is still considerable opportunity for increased utilisation of oral chemotherapy in the treatment of children with cancer. With the judicious application of such agents and the availability of more agents that can be given orally, the advantages of oral chemotherapy over parenteral treatment can be realised in more patients than is now the case. There are also solutions to the problems of refusal to take oral medication[18] and of administration constraints, such as capsule-swallowing training programmes.[19] The problem of adherence can be lessened through patient and parent education, nursing

intervention, frequent patient contact, and behavioural modification.[20-23] The lack of oral formulations is a problem that the pharmaceutical industry can solve. The industry is therefore urged to develop additional oral agents. Parenteral therapy will always have to be a major part of chemotherapy in children, but for the reasons elaborated in this review, oral chemotherapy can be used more than it is now prescribed.

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