Oral fludarabine

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Fludarabine is an antimetabolite cytotoxic agent uses for the treatment of patients with various lymphoid malignancies, especially B-cell chronic lymphocytic leukemia (CLL).[1] The intravenous formulation of fludarabine has been available for a number of years. It is well established as an effective first-line treatment option in CLL and preferred second-line therapy for patients with CLL initially treated with an alkylating agent-based regimen.[2-4] Intravenous fludarabine had been administered as an infusion for 5 consecutive days each month for about 6 months. This schedule creates a number of difficulties with respect to convenience with repeated venipunctures and frequent outpatient visits or hospital admissions.

Thus, an oral formulation would be more convenient for healthcare workers and patients, the majority of whom are elderly, often with poor venous access. In addition, due to potentially lower administration costs, oral fludarabine may be more cost effective than IV therapy.

An oral formulation of fludarabine has been developed, comprising 10 mg fludarabine in an immediate release tablet. It has become available, first in the UK, then in the majority of other European countries and Canada, for the treatment of patients with B-CLL after initial therapy with an alkylating agent-containing regimen has failed.[5] Oral fludarabine is typically given at a dosage of 40 mg/m^2 (7-8 tablets) once daily for 5 days, repeated every 4 weeks for up to six cycles. In September 2001, the UK National Institute for Clinical Excellence (NICE) endorsed the second-line use of oral fludarabine for the treatment of CLL.[6] NICE recommends oral fludarabine in preference to IV fludarabine on the basis of more favourable cost effectiveness and stated that IV fludarabine should only be uses when oral fludarabine is contraindicated. Nevertheless, there are issues regarding compliance as with any oral medication.

Pharmacodynamic and pharmacokinetic profile

Fludarabine is a purine (adenine) nucleoside analogue and a member of the antimetabolite class of cytotoxic drugs.[7] It is a synthetic prodrug that is rapidly dephosphorylated to F-ara-A by serum phosphatases. F-ara-A is the main plasma metabolite of fludarabine evaluated in pharmacokinetic analyses. F-ara-A is able to enter cells where it undergoes phosphorylation to form the active moiety, F-ara-A triphosphate (F-ara-ATP).

The dominant mechanism of action of F-ara-ATP is inhibition of DNA synthesis, although effects of RNA synthesis also contribute to inhibition of cell growth. Apoptosis may occur in both replicating and quiescent CLL cells.

DNA synthesis is inhibited by a number of actions of F-ara-ATP. Incorporation of F-ara-ATP into elongating nucleic acid chains results in the termination of DNA synthesis. F-ara-ATP is both a poor substrate for elongation and resistant to removal by DNA polymerases involved in DNA replication and repair. Priming of DNA synthesis and the joining together of DNA pieces are processes disrupted by F-ara-ATP through inhibition of DNA primase and DNA ligase. In addition, by inhibiting ribonucleotide reductase, F-ara-ATP reduces the cellular level of substrates for DNA polymerase required for DNA replication and repair with which it competes for incorporation into DNA.

Pharmacokinetic studies in patients with cancer confirm that single doses of oral fludarabine results in dose-dependent increases in maximum plasma concentration (C_{max}) and 24-h area under the concentration-time curve (AUC_{0-24h}).[8] Similar mean AUC_{0-24h} values were achieved with a 90 mg oral dose of fludarabine as with a 50 mg IV dose, but mean C_{max} values were approximately 20-30% lower compared with the corresponding values for the IV formulation.[9,10] The time to reach C_{max} is independent of dose. The bioavailability of oral fludarabine

is approximately 51-55% following single and multiple-dose administration with low intraindividual variation.[11] Systemic bioavailability, C_{max} and time to C_{max} are increased slightly (<10%) with concomitant food intake.[12] The terminal half-life is unaffected. These, and other pharmacokinetic studies have shown that a once-daily oral fludarabine dose of 40 mg/m^2 would provide a similar systemic exposure to fludarabine IV.[7, 13, 14]

Therapeutic trials

We evaluated in a prospective, multicentre phase II study the clinical efficacy of oral fludarabine 40 mg/m^2/day for 5 days every 4 weeks for 6-8 cycles as second-line therapy in patients with B-CLL.[15] The intention-to-treat population comprised 78 relapsed or refractory patients, all had been previously treated with one or more regimens including an alkylating agent. According to IWCLL criteria, the overall response rate was 46.2% (95%CI 34.8-57.8%); 20.5% an 25.6% of patients achieved CR and PR, respectively. Using NCI criteria, the overall response rate was slightly higher. Results of this study showed that patients with less advanced disease had higher overall response rates than those with more advanced disease (Binet C). The optimal duration of therapy was six cycles for most patients and WHO performance status was either improved (15.4%) or remained unchanged (55.1%). These data suggests that the benefits of oral fludarabine extend beyond blood cell responses and have a positive impact on quality of life. These results were comparable with data from the historical cohort.

The tolerability profile of oral fludarabine in the second-line treatment of CLL was comparable to that of the IV formulation, with the exception of more frequent gastrointestinal toxicity. Nausea/vomiting and diarrhea each occurred in 38.5% of patients, although no patient stopped treatment as a result of these complications. The majority of these events were WHO grade 1 and 2, with only a single case of Grade 3 nausea and three reports of grade 3 diarrhea. GI toxicity is important when evaluating oral agents because vomiting or diarrhea may prevent accurate dosing, thereby affecting drug serum levels. The most common adverse effect during oral fludarabine treatment was myelosuppression including WHO grade 3 and 4 granulocytopenia, thrombocytopenia and anemia. 25.6% of patients required dose reductions due to haematological toxicity. Autoimmune haemolytic anemia was noted in four patients with three requiring hospitalization. All of these patients responded to corticosteroids. Infection was common and occurred in 44.9% of patients. Alopecia and skin rashes were rare events. This key study confirms that oral fludarabine is as effective and well tolerated as IV fludarabine in the second-line treatment of CLL. Gastrointestinal toxicity is higher with the oral formulation but does generally not require treatment and infusion-related adverse events are eliminated.

Oral fludarabine as first-line treatment for CLL has also been studied.[16] Rossi *et al.,* evaluated in a multicentre, open label study in 81 previously untreated CLL patients the effectiveness of oral 40 mg/m^2 fludarabine per day for 5 days every 4 weeks for 6-8 cycles. 18.5% of patients were stage Binet A, 63% stage B and 18.5% stage C. The overall response rate was 71.6% according to IWCLL criteria (37% CR, 34.6% PR) and 80.2% using NCI criteria and was comparable with that achieved in a similar historical cohort who received first-line therapy with IV fludarabine. Response was related to disease stage. WHO performance status improved in 13.6% of patients and remained unchanged in 77.8%. As in the previous study, the majority of side effects were mild-to-moderate intensity, manageable and reversible. GI toxicity was more common with the oral formulation but did not require treatment in the majority of patients.

These findings are supported by an additional but smaller study.[17]

Oral fludarabine combination therapy as first-line treatment for CLL has also been evaluated.[18] In an open-label study, 75 treatment-naïve patients with CLL received oral fludarabine 30 mg/m^2 plus oral cyclophosphamide 200 mg/m^2/day, on days 1-5 every 28 days for 6 cycles. OR rate (NCI criteria) was 79.9%, including 49.3% CR, nodular PR of 5.3% and 25.3% PR. Toxicity was mainly haematological and included NCI grade 3-4 lymphopenia (79% of cycles), neutropenia (52%), thrombocytopenia (6%) and anemia (3%). The incidence of infection was low and GI disturbances were mild and included nausea (grade 1-2, 75%; grade 3-4, 7%) and vomiting (grade 1-2, 37%; grade 3-4, 3%).

Conclusions

These studies demonstrate that the efficacy and tolerability of oral fludarabine is essentially similar to IV formulation, either alone or as part of combination therapy.

The efficacy has been demonstrated for both first- and second-line therapy, with OR rates of 72-80%, and 46-51%, respectively. Consequently, oral fludarabine has recently become available in the majority of European countries and Canada for the second-line treatment of CLL. Guidelines from NICE in the UK recommend oral fludarabine as second-line therapy for patients with CLL who have failed, or tolerant of, first-line chemotherapy, and who would otherwise have received combination chemotherapy with cyclophosphamide-based regimens. The NICE guidelines found the oral formulation to be more cost effective than

intravenous fludarabine, and suggested that oral fludarabine is more likely to be acceptable to patients and caregivers because it can be administered on an outpatient basis and may reduce the need for hospital visits. In particular, the convenience of oral administration has the potential to significantly improve patients' QoL.

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