Drugs 2003; 63 (21): 2324-2325
0012-6667/03/0021-2324/$33.00/0

Oral Fludarabine

A Viewpoint by Dieter Huhn

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In recent years an oral formulation of fludarabine has been developed (10mg immediate-release tablet). This oral formulation has been available in all EU states since 2001/2002 with the exception of Belgium, Germany and Portugal. In this commentary, the following question will be addressed: are there any advantages, or are there any disadvantages of the oral formulation when compared with its intravenous counterpart?

Pharmacokinetic studies[1] have demonstrated that a once-daily oral dose of 40 mg/m^2 will provide a similar systemic exposure to 25 mg/m^2/day given intravenously. The systemic availability (approximately 55%) is dose-independent, the bioavailability ranges from 30–80% between patients, the intraindividual variation in bioavailability is low and is not affected by a high-fat meal.

These promising pharmacokinetic data have been supported by clinical data from a phase II trial. Seventy-eight patients received oral fludarabine 40 mg/m^2/day for 5 days every 4 weeks for six to eight cycles as a second-line therapy in B-cell chronic lymphocytic leukaemia (CLL).[2] Reference to an historical group of comparable patients treated with the intravenous formulation allowed a comparison of the two formulations. This study showed that oral fludarabine has similar clinical efficacy and a similar tolerability profile when compared with the intravenous formulation.

When comparing an oral and an intravenous formulation, gastrointestinal adverse effects are of particular relevance, because vomiting or diarrhoea may prevent accurate dosing and because patients are averse to nauseating medications. Nausea and vomiting, as well as diarrhoea, occurred in 38% of patients in the phase II trial.[2] However, the gastrointestinal adverse events were generally mild to moderate in severity, with only one single instance of WHO grade 3 nausea and three cases of WHO grade 3 diarrhoea. (Unfortunately, the use of antiemetics was not specified, but was left to the investigator's discretion.) Nevertheless, there were no withdrawals from the study because of vomiting or diarrhoea.

In conclusion, the oral formulation of fludarabine is characterised by predictable and safe pharmacokinetic properties with clinical equivalence and an essentially similar safety profile when compared with the intravenous formulation. So, no disadvantages of this oral formulation can be recognised.

But are there any advantages to the patient? Fludarabine is mainly administered in the outpatient setting. Therefore, when using the oral formulation, visits to the outpatient department can be reduced and intravenous infusions can be avoided. It should be kept in mind that in rare cases a tumour lysis syndrome can be induced by fludarabine. Therefore, a close check-up of the patients even after oral fludarabine therapy is recommended. Nevertheless, the oral formulation will be more cost effective than intravenous fludarabine. This obvious advantage to the patient can be transformed into a disadvantage to the oncologist: reimbursement for intravenous chemotherapy by insurance companies is disproportionately higher when compared with oral therapy, at least in Germany. But, hopefully, the application of oral fludarabine will not be hampered by unreasonable regulations of insurance companies! ▲

References

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