

## Letters to the Editor

**Correspondence re: V. I. Avramis *et al.*, Pharmacokinetic and pharmacodynamic studies of fludarabine and cytosine arabinoside administered as loading boluses followed by continuous infusions after a Phase I/II study in pediatric patients with relapsed leukemias. *Clin. Cancer Res.*, 4: 45–52, 1998.**

### Fludarabine: Phosphate or No Phosphate, That Is the Confusion

#### Letter

In the 1960s, “fludarabine” (F-araA,<sup>1</sup> NSC 118218) was synthesized and shown to have *in vitro* cytotoxicity (1). By the early 1980s, “fludarabine phosphate” (F-araAMP, NSC 312887) had been synthesized, and this water-soluble form is what is now commonly administered to patients with chronic lymphocytic leukemia at 25 mg/m<sup>2</sup> for 5 days every 4 weeks (2). In plasma, F-araAMP is rapidly dephosphorylated to F-araA, which is taken up by cells and rephosphorylated to F-araAMP and then to F-araATP (3).

However, for the last decade, patients, doctors, and researchers have used the name fludarabine synonymously with fludarabine phosphate to mean F-araAMP. This can lead to some confusion as to what the name fludarabine actually refers to, and Avramis *et al.* (3) have fallen into this trap. The title of their paper refers to “fludarabine and cytosine arabinoside administered. . .” In the abstract, the terms fludarabine and fludarabine phosphate were both used to mean F-araAMP, and 9-β-D-arabinofuranosyl 2-fluoroadenine was used to mean the metabolite F-araA. However, fludarabine was also used once when the context suggested F-araA. Finally, the word fludarabine referring to F-araAMP was negated by the (terminologically correct) abbreviations footnote, where F-araAMP was defined as fludarabine phosphate, and F-araA was defined as fludarabine (suggesting that the drug given to patients was F-araA).

Despite all those “in the field” knowing what is meant, these problems with nomenclature are widespread. For example, Bai *et al.* (4) state that “9-β-D-arabinofuranosyl-2-fluoroadenine (2-F-ara-A) is the main metabolite of fludarabine”; *The Cytotoxic Handbook* (5) suggests that both fludarabine and fludarabine phosphate are approved names; and *The Chemotherapy Source Book* uses the names interchangeably (6). A literature search of fludarabine retrieved only 28 of 464 (6%) papers (inconsistently) using the INN fludarabine phosphate anywhere in the title or abstract.

This must be confusing for those who are new to the field. It could be of particular importance in the pharmacy, where confusion between F-araA and F-araAMP could lead to a pre-

scription for 25 mg/m<sup>2</sup> fludarabine being administered as 32 mg/m<sup>2</sup> fludarabine phosphate, a 28% overdose. (Could this have been the cause of a few of the occasionally severe side effects observed with fludarabine?) In the laboratory, a 28% error in concentration could lead to dubious results.

Other cytotoxic drugs, such as doxorubicin hydrochloride and vincristine sulfate, present a similar problem. However, here the potential confusion and overdose are considerably smaller because, for instance, doxorubicin is not a metabolite of the administered drug, and there is only a 6% difference in molecular weight between doxorubicin and doxorubicin hydrochloride.

Beginning January 1999, various drug names will be standardized throughout the world. For example, the name adrenaline, which is prevalent in the United Kingdom, will be replaced by the INN epinephrine. Is it not time to officially change the INN of F-araAMP to the commonly accepted name fludarabine and refer to the metabolites as F-araA and F-araATP? We would then no longer administer fludarabine and have it dephosphorylated in the plasma to fludarabine.

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#### References

1. Montgomery, J. A., and Hewson, K. Nucleosides of 2-fluoroadenine. *J. Med. Chem.*, 12: 498–504, 1969.
2. The French Cooperative Group on CLL, Johnson, S. A., Smith, A. G., Loffler, H., Osby, E., Juliusson, G., Emmerich, B., Wyld, P. J., and Hiddemann, W. Multicentre prospective randomised trial of fludarabine *versus* cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukaemia. *Lancet*, 347: 1432–1438, 1996.
3. Avramis, V. I., Wiersma, S., Krailo, M. D., Ramilo-Torno, L. V., Sharpe, A., Liu-Mares, W., Kowck, R., Reaman, G. H., and Sato, J. K. for the Children's Cancer Group. Pharmacokinetic and pharmacodynamic studies of fludarabine and cytosine arabinoside administered as loading boluses followed by continuous infusions after a Phase I/II study in pediatric patients with relapsed leukemias. *Clin. Cancer Res.*, 4: 45–52, 1998.
4. Bai, L., Yamaguchi, M., Tatsumi, M., Kon, K., and Brautigam, M. Mechanisms responsible for resistance of sublines derived from leuke-

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<sup>1</sup> The abbreviations used are: F-araA, 9-β-D-arabinofuranosyl-2-fluoroadenine; F-araAMP, 9-β-D-arabinofuranosyl-2-fluoroadenine-5'-monophosphate; F-araATP, 9-β-D-arabinofuranosyl-2-fluoroadenine-5'-triphosphate; INN, International Non-Proprietary Name.

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mia cell lines to an antitumor agent 9- $\beta$ -D-arabinofuranosyl-2-fluoroadenine. *J. Cancer Res. Clin. Oncol.*, 124: 367–373, 1998.

5. Allwood, M., Stanley, A., and Wright, P. *The Cytotoxics Handbook*, Ed. 3, pp. 260–261. Oxford: Radcliffe Medical Press, 1997.

6. Perry, M. C. *The Chemotherapy Source Book*, pp. 451–452. Baltimore: Williams & Wilkins, 1992.

## Reply

I thank Dr. Bosanquet for his keen observation (1). However, literature tends to confirm, at first by acceptable agreement of the investigators in the field and later by some convention, abbreviations of chemicals that eventually become licensed drug products.

Examining the research literature on this very important antileukemic drug, one will find a number of preclinical studies in tumor-bearing animals from the early 1980s that examined the biochemical pharmacology of both the relatively insoluble F-araA<sup>1</sup> (fludarabine) and its soluble derivative 5'-monophosphate as the Na<sup>+</sup> salt (NSC 312887; Refs. 2 and 3). This product is licensed by the Food and Drug Administration under the brand name Fludara and is the only formulation administered to all patients all over the world. This information is clearly stated in the first paragraph of the introduction of our paper (4), with the appropriate references.

These studies in animals clearly showed the metabolic fate of F-araAMP in an *in vivo* mammal system and the advantages of using the soluble form of the drug for ease of administration. Thus, the administered form of this drug, F-araAMP (Na<sup>+</sup> salt), very rapidly becomes F-araA in plasma in patients; hence, the name fludarabine is used. Assuming that someone had not already examined the early literature, it is rather difficult, as I discovered, to persuade my fellows to go back and perform a complete literature search of a subject beyond an electronic search in a computerized data base. However, it is abundantly clear that, in addition to our manuscript, the term "fludarabine" was used in a 1996 publication (3) without any confusion to leukemologists, including both clinical investigators and basic scientists. This is due to the understanding that the administered formulation is F-araAMP (Na<sup>+</sup> salt) at the dose prescribed and that the prodrug circulating in the bloodstream is F-araA as an equimolar (not equimilligram) dose.

In addition to the parallel examples that the author states, I would add the example of prescribing "morphine" *versus* mor-

phine sulfate. I do not believe that any physician or pharmacist would be "confused," as Bosanquet suggests (1), and adjust the dose, resulting in an overdose by morphine.

For us to have said "PK [pharmacokinetic] and PD [pharmacodynamic] studies of fludarabine phosphate..." without presenting such pharmacokinetic evidence of dephosphorylation in these patients would have been a scientific error. Therefore, we agree with the majority of our colleagues who have published in literature on the subject and use the term fludarabine as the abbreviation of the pharmacological molecule that circulates in plasma and is uptaken by the leukemic cells exerting its antileukemic effect.

Finally, regarding the Bosanquet's "question" and/or suggestion that the cause of "the occasionally severe side effects observed with fludarabine" (1); unless the author has direct evidence, there is no justification, ethically, to attribute a 28% dosing error of this drug to the pharmacy. At any rate, this paragraph strongly indicates that the known inter- and inpatient variabilities that accompany this drug's anabolism in leukemia patients is apparently ignored by Bosanquet (1).

In conclusion, we should be sensitive to potential confusions and use the proper term, *i.e.*, fludarabine phosphate as the licensed and administered drug and, conceptually, the term fludarabine as the molecular entity that, as a prodrug, exhibits its antileukemic and toxic effects.

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## References

1. Bosanquet, A. L. Fludarabine: phosphate or no phosphate, that is the confusion. Correspondence re: V. I. Avramis *et al.*, Pharmacokinetic and pharmacodynamic studies of fludarabine and cytosine arabinoside administered as loading boluses followed by continuous infusions after a Phase I/II study in pediatric patients with relapsed leukemias. *Clin. Cancer Res.*, 4: 45–52, 1998. *Clin. Cancer Res.*, 5: 475, 1999.
2. Avramis, V. I., and Plunkett, W. Metabolism and therapeutic efficacy of 9- $\beta$ -D-arabinofuranosyl-2-fluoroadenine against murine leukemia P388. *Cancer Res.*, 42: 2587–2591, 1982.
3. Avramis, V. I., and Plunkett, W. Metabolism of 9- $\beta$ -D-arabinofuranosyl-2-fluoroadenine 5'-phosphate by mice bearing P388 leukemia. *Cancer Drug Deliv.*, 1: 1–10, 1983.
4. Avramis, V. I., Wiersma, S., Krailo, M. D., Ramilo-Torno, L. V., Sharpe, A., Liu-Mares, W., Kowck, R., Reaman, L. H., and Sato, J. K. for the Children's Cancer Group. Pharmacokinetic and pharmacodynamic studies of fludarabine and cytosine arabinoside administered as loading boluses followed by continuous infusions after a Phase I/II study in pediatric patients with relapsed leukemias. *Clin. Cancer Res.*, 4: 45–52, 1998.

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