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LETTER TO THE EDITORS

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Use of PEG-asparaginase in the treatment of patients with solid tumors

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Sir, PEG-asparaginase is the polyethylene glycol conjugated form of the drug asparaginase that has long been recognized as an essential element of well-proven efficacy of schedules used in the treatment of acute lymphoblastic leukaemia (ALL). In vitro as well as in vivo investigations on the use of PEG-asparaginase in the treatment of solid tumors have recently been reported [7].

Asparaginase is an asparagine-degrading enzyme that depletes the blood pool of this usually non-essential amino acid. The postulated antineoplastic effect of asparaginase has been suggested to be related to a reduced expression of the enzyme asparagine-synthetase which has been observed in sensitive lymphoblastic blast cells.

The results of in vitro toxicity tests performed by Taylor et al. [7] show that some solid tumor entities are highly sensitive to high concentrations of PEG-asparaginase. The authors suggest from these observations that PEG-asparaginase may have shown antitumor activity against the tested specimens. However, in the interpretation of in vitro data one has to consider that glutamine, like asparagine, also serves as substrate. As a consequence of the high concentrations of asparaginase, the medium is rapidly depleted of asparagine and ongoing catalytic activity leads to a decrease in glutamine with a significant increase in glutamic acid and ammonia [8, 9]. Such alterations in the culture medium may thus contribute to or be responsible for the cytotoxic effects. In vitro tests also have to be discussed in relation to the clinical evaluation of the drug. None of the treated patients with solid tumors showed a partial or complete response following repeated administrations of PEG-asparaginase, whereas low in vitro sensitivity observed in non-Hodgkin lymphoma (NHL) specimens contrasts with the fact that asparaginase is well established in treatment regimens for NHL.

These profound differences indicate that the in vivo relevance of in vitro toxicity assays involving asparaginase has to be interpreted with caution. Apart from using asparagine-free cell culture conditions, the determination of asparagine-synthetase expression patterns of the tested specimens might offer a useful alternative. Neither asparaginase in vitro cytotoxicity nor asparagine-synthetase, however, have been validated as surrogate parameters for clinical response.

The severity and spectrum of adverse effects occurring after PEG-asparaginase administration were comparable to those reported with native asparaginases, a finding which has also been reported by others [2]. Of 28 patients, 2 experienced severe side effects in the phase I trial performed by Taylor et al. [7]. Adding to these findings the lack of data supporting a tumor response to PEG-asparaginase in solid malignancies, which confirms experiences from the early years of clinical evaluation of the native asparaginase [1, 6], a rationale proposing future trials with asparaginase-containing regimens in patients with advanced-stage solid malignancies has to be critically reviewed.

Concentrations of asparagine, the main pharmacodynamic target, were measured in the context of administering different dose levels of PEG-asparaginase. Recovery of asparagine was reported to be lowest at the highest dose level of 2000 IU/m^2 [7]. However, concentrations of asparagine were detectable in relevant amounts prior to the administration of PEG-asparaginase independent of the dose level applied. From a pharmacological point of view, a continuous depletion of asparagine without intermittent feeding of sensitive malignant cells is assumed to be the major antitumor effect. Investigations on the pharmacokinetics of PEG-asparaginase performed at

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our institution have demonstrated high interindividual variability of measured asparaginase activities [4] and, as a result, relevant differences in the persistence of activity values > 100 IU/l which have been postulated to ensure complete asparagine depletion in serum and CSF [5]. Following treatment with 1000 IU/m^2 PEG-asparaginase, a considerable number of children have failed to show activities of > 100 IU/l over a period of 2 weeks, which was associated with reduced treatment intensity.

Further, we have observed that the kinetics of the activity time course of PEG-asparaginase can be described by a Michaelis-Menten rather than a linear model [4]. Therefore, increasing the dose would not be expected to cause a significant prolongation of the therapeutic time period. Preliminary analysis of data from children on 2500 IU/m^2 PEG-asparaginase seems to confirm these expectations. Still, the phenomenon of silent inactivation has to be taken into account when asparaginase is to be administered repetitively. Anti-asparaginase antibody formation may occur without clinical manifestations, but alters the pharmacokinetics of the enzyme resulting in suboptimal asparagine depletion [3]. Thus, an appropriate schedule for PEG-asparaginase will need to allow for the pharmacokinetic properties of the enzyme. Depending on the desired end-point, changing the interval between administrations seems to be preferred to increasing the dosage if a longer period of treatment with PEG-asparaginase is intended. Drug monitoring is a useful tool for estimating interindividual differences and also for detecting patients with silent inactivation.

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