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Intratumoral measurement and plasma pharmacokinetics of intravenously administered Melphalan

Report of a patient with plasmacytoma

Sten Friberg[1], Hans Ehrsson[2], Staffan Eksborg[2], and Christer Carenfeldt[3]

[1] Department of General Oncology, Danderyd's Hospital, S-18288 Danderyd, Sweden
[2] Karolinska Pharmacy, Box 60024, S-10401 Stockholm, Sweden
[3] Department of Otorhinolaryngology, Karolinska Hospital, S-10401 Stockholm, Sweden

Summary. In a human case of plasmacytoma we studied plasma and tumor concentrations of melphalan given intravenously. Intratumoral concentration of melphalan was similar to plasma concentration 60 min after the end of infusion.

Introduction

The pharmacokinetics of cytotoxic drugs in humans have previously been studied primarily with regard to plasma levels, rarely in the tumor itself. Few malignancies are available for visual follow-up and reiterated sampling. Oral and oropharyngeal tumors provide this opportunity.

Plasmacytoma in the oropharyngeal region is a rare entity. We report here on the intratumoral concentration of melphalan given i.v. in one such case.

Materials and methods

Case report: The patient – male, 78 years old – presented at the ENT department complaining of a lump in the throat. Examination revealed two separate tumors: one, measuring $5 \times 2.5 \times 2$ cm, in the left tonsillar region, the other ($1.5 \times 1.5 \times 1.5$ cm) in the left vallecula. Both tumors were covered by intact mucosa. Surgical biopsies were taken from both. Microscopically, the tissues were massively infiltrated by atypical plasma cells staining positively for kappa IgG. The picture was compatible with plasmacytoma.

Neither clinically nor radiologically could any other manifestations of the disease be detected: a sternal puncture was negative, as were electrophoreses of serum and urine. All routine hematological and biochemical tests were normal. The patient was considered to have an extramedullary plasmacytoma stage I.

Clinical considerations: Since the patient had two separate tumors, a generalized disease could not be excluded in spite of the negative tests. General chemotherapy was therefore preferred to local radiotherapy.

The fact that the patient had two separate, directly visible and easily accessible tumors provided us with a unique opportunity for the study of solid malignancies: during generalized treatment, one tumor could be subjected to analysis, while the other – surgically unharmed – could serve as an indicator of the efficacy of treatment. Written consent was obtained from the patient. One of us (C. C.) has permission from the local ethical committee to obtain biopsies from oral tumors.

Treatment: Melphalan (Alkeran)/prednisolone (Deltison) was chosen for treatment [3]; 0.10 mg/kg/day and 50 mg/day respectively were given for 4 consecutive days. Melphalan was given as an i.v. infusion during 30 min. Prednisolone was given orally. The course was repeated in 28-day cycles.

Plasma samples: Blood samples (5–7 ml) were collected in glass test tubes (Vacutainer) containing 250 IU heparin, freeze-dried and immediately placed on ice. After centrifugation (4° C) the plasma fraction was removed and stored at −20° C until analysis.

Blood samples were taken at 5, 15 and 30 min during the infusion, and also 5, 15 and 30 min and 1, 2, 3, 4 and 6 h after the end of the infusion.

Determination of melphalan: The plasma concentration of melphalan was determined by reversed phase liquid chromatography using fluorometric (260/360 nm) detection after derivatization of melphalan with *N*-acetylcysteine [5].

The tumor was biopsied 60 min after completion of the infusion and the specimen processed as follows. Tumor (0.35 g) was homogenized with 0.5 ml PBS using a Polytron homogenizer. The suspension was divided into three parts: one was used to determine melphalan concentration; one was left at 37° C for 24 h to assure complete degradation of melphalan ($t\ ½ \sim 2$ h [1] followed by addition of a known amount of melphalan (reference sample); and one was left at 37° C for 24 h and served as a blank. Melphalan concentration was measured using the technique described above.

Results

The patient was given six courses of melphalan/prednisolone. No plasma samples or tumor biopsy specimens were taken during these courses. The first signs of regression were noticed after the sixth course. It was therefore decided to take plasma samples and a tumor biopsy specimen during the seventh course.

Offprint requests to: S. Friberg

In order to estimate the optimal interval between the infusion of melphalan and tumor biopsy, the plasma levels of melphalan (without the addition of prednisolone) were studied in a "pretest". Prior to the regular seventh course, 7 mg of melphalan was given as an infusion as described. Blood samples were drawn at indicated intervals. The results are shown in Fig. 1.

To see if the addition of prednisolone influenced the pharmacokinetics of melphalan, a second curve of plasma concentrations was obtained on day 1 of the seventh course. The curve is also shown in Fig. 1. The tumor biopsy was obtained on day 4 during the same course of chemotherapy. Plasma samples were also taken on day 4. By that time the larger tumor had diminished to $1 \times 1 \times 1$ cm. The sensitivity of the analytical procedure and limited tumor mass (0.35 g) allowed for only one single analysis of the tumor concentration of melphalan. The results are shown in Fig. 1.

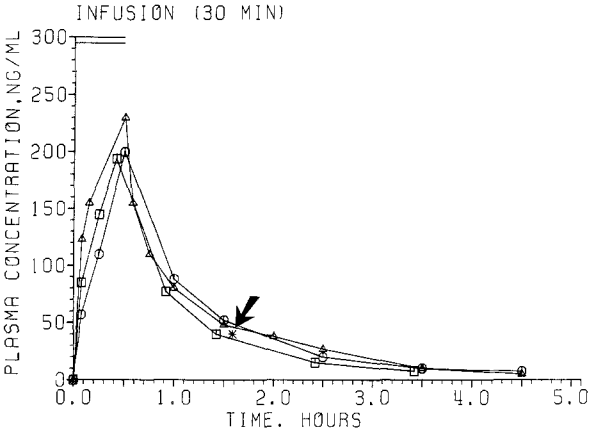

Fig. 1. Plasma concentrations of melphalan versus time on three different occasions. Δ——Δ = "Pretest": 7 mg of melphalan given i. v. without the addition of prednisolone. 0——0 = Melphalan concentrations on day 1 of a regular course, with prednisolone added. □——□ = melphalan concentrations of day 4 of a regular course. *Thick arrow* indicates concentration in the tumor biopsy

Table 1. Maximum plasma concentration (C_{max}) and area under the plasma concentration curve (AUC_4^0)[a] of melphalan

Time	C_{max} (μg/ml)	AUC_4^0 (μg × min × ml^{-1})[b]	$t_{1/2}\beta$ (min)
Pretest: without prednisolone	0.23	14.0	52.5
Day 1: with prednisolone	0.20	13.2	73.0
Day 4: with prednisolone	0.19	11.2	55.6

[a] The AUC was calculated from the start of the infusion to 4 h post infusion by the trapezoidal method

[b] The concentration of melphalan after 6 h was <5 ng/ml

The plasma pharmacokinetics of melphalan during these three consecutive courses were similar (Fig. 1, Table I).

The intratumoral concentration of melphalan (41 ng/g) was similar to the plasma concentration (40 ng/ml) 60 min after the end of the infusion.

Although the biopsy included all visible remaining parts of the initially larger tumor, no parts could be spared for histology, since the chemical analysis required all excised tissue. The smaller tumor was left intact. No normal tissue was analyzed.

The initially smaller tumor had vanished macroscopically one month later. Biopsies were taken from the region were it had been located. Microscopically, no atypical plasma cells were found.

The patient has been followed up for 2 years since the last course of chemotherapy. There have been no signs of recurrence or progression.

Discussion

The curves from the three serial analyses of repeated infusions of melphalan are very similar. Evidently, the addition of prednisolone did not affect the pharmacokinetics of melphalan in this patient. The elimination half-life of melphalan is in accordance with previous findings after i.v. administration [2]. The intratumoral concentration of melphalan 60 min after the end of infusion is similar to the plasma level. A rapid uptake of melphalan has previously been observed in rodent tumors in vivo [4]. Thus, there is no diffusion barrier between serum and tumor cells in this case. Since we could obtain only a single tumor biopsy, detailed intratumoral pharmacokinetics could not be studied.

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