Chemotherapy Studies in Autochthonous Rat Tumors

Intestinal Cancer

F. Sych, M. Habs, and D. Schmähl
Institute of Toxicology and Chemotherapy (Director: Prof. Dr. D. Schmähl), German Cancer Research Center, Im Neuenheimer Feld 280, 6900 Heidelberg, Federal Republic of Germany

Summary. Intestinal tumors in rats were induced by three different chemical carcinogens. Only tumors induced by 1,2-dimethylhydrazine responded slightly to combination chemotherapy of Adriamycin, Methotrexate, 5-Fluorouracil, and Cyclophosphamide. The same therapy failed in tumors induced by N-methyl-N'-nitro-N-nitroso-guanidine or acetoxymethyl-methyl-nitrosamine. These results and the comparability of chemotherapy in autochthonous tumors to experimental and clinical observations are discussed.

Key words: Intestinal tumors — Experimental carcinogenesis — Chemical carcinogens — Combined chemotherapy

Chemotherapeutische Untersuchungen an autochthonen Tumoren der Ratte — Darmkrebs


Schlüsselwörter: Darmtumoren — Experimentelle Karzinogenese — Chemische Karzinogene — Kombinationschemotherapie

Intestinal cancer is one of the most frequent malignancies in the Western world (cf. UICC, 1973). In respect to etiology, environmental factors play the major role in human cancer (cf. Schmähl, 1970). This was also demonstrated in colon cancer (cf. Reddy et al., 1977). Beside others, Schmähl (1966, 1970) postulated to use...
chemically induced autochthonous tumors as predictive tests for clinical chemotherapy. Previous results showed that chemotherapy of these tumors are more reliable and comparable to human situation than studies in established transplanted tumor systems (cf. Fiebig and Schmähl, 1977a; Fiebig and Schmähl, 1977b; Fretz et al., 1969; Habs et al., 1977a; Habs et al., 1977b; Schmähl et al., 1963; Schmähl and Schrick, 1964; Schmähl et al., 1966; Schmähl et al., 1968; Storch et al., 1977).

Since tumors of the gut can be induced by different methods and numerous carcinogens (cf. Reddy et al., 1975; Weisburger, 1971; Wynder and Reddy, 1973), an optimal tumor model has to be selected. In comparison with human disease the tumors should be predominantly localized in the colon and rectum, they should appear as adenocarcinomas with high metastatic potency; the tumors should occur in the target organ only in high morbidity after a short induction period.

After subcutaneous applications of 1,2-dimethylhydrazine (DMH) particularly tumors of the gut are observed, in less frequency in addition tumors of the ear duct, liver and kidney are found (cf. Druckrey et al., 1967; Schmähl et al., 1976). By rectal instillations of N-methyl-N'-nitro-N-nitroso-guanidine (MNNG) tumors are induced locally between the left colonic flexure and the anus only (cf. Narisawa et al., 1971). While DMH-induced tumors metastasize frequently, this is not described for MNNG-induced tumors. Acetoxymethyl-methyl-nitrosamine (AMMN) showed a strong local carcinogenic activity after oral applications (Wiessler and Schmähl, 1976). Therefore, it was given intrarectally in this experiment hoping to find the same unequivocal local activity.

Exploratory laparotomy served for tumor diagnosis, as described in previous experiments (Habs et al., 1977a; Habs et al., 1977b). As in these experiments drugs of high clinical effectiveness (cf. Wassermann et al., 1975) were applied in combination chemotherapy at different dose levels.

Material and Methods

1. Animals

Male Wistar rats (Ivanovas, Kißlegg), weighing about 175 g at the start of the experiment, were kept under conventional conditions. They were fed with Altromin-pellets and tap-water ad libitum.

2. Experimental Groups

367 rats received carcinogen-treatment (DMH: 120 rats, MNNG: 123, AMMN: 124). Three solvent-treated control groups were formed by a total of 79 animals (DMH-C: 28 rats, MNNG-C: 27, AMMN-C: 24). Hematological and enzyme chemical control values were obtained from these rats.

3. Carcinogens

DMH was provided by M.Wiessler as dihydrochloride salt. It was dissolved in physiological saline adjusted to pH 6.5 by sodium bicarbonate and applied subcu-