

ANTI-TUMOUR EFFECT OF AN AROMATIC RETINOIC ACID ANALOG IN A MOUSE SYNGENEIC TRANSPLANTABLE SARCOMA

SUMMARY

Anti-tumour activity of an aromatic retinoic acid analog has been tested on Sarcoma J in syngeneic system. Tumour complete regression rate and median survival time of progressors mice are significantly improved. These results are at variance with previous observations suggesting the lack of activity of this compound on transplanted murine tumours. Arguments in favour of an immunological stimulation responsible for the observed anti-tumour effect are presented and discussed.

RÉSUMÉ

L'effet anti-tumoral d'un analogue aromatique de l'acide rétinoïque a été étudié sur le Sarcome J en système syngénique. Le taux de régressions tumorales complètes et la survie moyenne des animaux « progressseurs » sont significativement augmentés.

Ces résultats contrastent avec les observations publiées antérieurement qui tendaient à établir le manque d'activité de cette substance sur les tumeurs murines transplantées. Des arguments sont avancés en faveur d'un mécanisme immuno-stimulant responsable de l'effet anti-tumoral.

Retinoids have been shown to exert both prophylactic and therapeutic effects against chemically

induced tumours in their primary host (2). However, no activity has been observed, up to now, on murine transplantable tumours. On the other side, immunostimulatory properties of vitamin A derivatives are also well established (7). We tested the possible effect of an aromatic retinoic acid analog* on Sarcoma J owing to the peculiar immune control mechanisms of this spontaneous tumour in syngeneic recipients.

Sarcoma J has spontaneously originated in a C57 Bl mouse. We are maintaining a tumour strain by subcutaneous transplantations at regular intervals. Growth patterns and immunological features have been previously extensively reported (1). C57 Bl females mice 2 months old were used as experiment animals.

Tumour grafts were inoculated intradermally in the medio-dorsal skin by means of a trochar. Evaluation of tumour growth was made at regular intervals until the death of the animals. Mice cured of a primary sarcoma received a second inoculation (10^6 cells) in order to challenge anti-tumour immunity.

Intraperitoneal injections of retinoic acid analog were made three times at weekly intervals (400 mg/kg/injection). Treatment was started eight days after tumour implantation. Control animals received intraperitoneal administration of the suspension agent in the form of arachid oil.

Under strict aseptic conditions the percentage of takes amounts to 100. Tumour development is purely

* Ro 10-9359 (ethyl-all-trans 9-4 methoxy-2, 3, 6-trimethylphenyl-3, 7-dimethyl-2, 4, 6, 8-nonatetraconate) was kindly supplied by « Produits Roche » Bruxelles (Belgium).

local without deep infiltration or visible metastases. After a phase of active growth, a stabilization period eventually occurs and a constant proportion of animals exhibit a complete tumour regression. Treatment with aromatic retinoic acid analog significantly improves the rate of complete tumour regression (60 % versus 40 % in controls). The median survival time of progressors mice rises from 22 days to 31 days. In animals cured of a primary tumour, the specific resistance towards a subsequent sarcomatous graft is also more important in the treated group (Table I).

TABLE I

Results of treatment of Sarcoma J with aromatic retinoic acid analog : complete regression rate, median survival time of progressors mice and rejection rate of tumour challenge graft in cured animals. (significant differences : * $p < 0.05$, ** $p < 0.01$)

| | Treated group | Control group |
|------------------------------------|----------------|-----------------|
| Sarcoma J complete regression rate | 60 % (27/45) | 40 % (19/47) |
| | * | * |
| Median survival of progressors | 31.1 ± 12 days | 22.6 ± 8.7 days |
| | ** | ** |
| Immunization of cured animals | 100 % (27/27) | 85 % (16/19) |

Retinoids have been shown to exert some anti-tumour effects. A preventive role was pointed out as regard skin, colon and bladder chemical carcinogenesis in mice and rats (4, 9). Induced skin carcinomas regressed to some extent in their primary host following administration of retinoic acid analog. However, this compound did not inhibit the growth of several transplanted tumours : Ehrlich carcinoma in solid and ascitic forms, Sarcoma 180 and leukemia L 1210 (2).

Present results are at variance with these observations as treatment significantly influences regression

rate of sarcoma J and survival of progressors animals. Our syngeneic transplantable tumour possesses clear-cut immunological control mechanisms and manipulation of host defenses sharply modifies growth pattern (1). This feature should be taken into account to explain discrepancies of activity according to tumour systems.

Direct inhibition of cell proliferation (6) might only constitute one aspect of retinoids effects. Recent reports have emphasized the importance of vitamin A analogs in immune resistance to tumours (5). In lung cancer patients, high dosage vitamin A therapy potentiates lymphocyte blastogenesis to PHA and delayed cutaneous hypersensitivity reactions (8). Moreover, retinoic acid has been shown to be a specific adjuvant for the induction of cytotoxic thymus derived lymphocytes (3).

In our experiment, mice cured of sarcoma J achieved a better antitumour immunity when treated with retinoic acid analog. The hypothesis of an immunological effect responsible for anti-tumour activity is presently under investigation.

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