Potentiation of the Cancerostatic Effect of 6-Azauridine and 6-Azacytidine with 5-Bis-(2-chloroethyl)aminomethyluracil

Recent clinical tests with 6-azauridine, carried out in this country, indicate that this drug may in some cases bring about remission of leukaemia as well as some degree of regression of certain solid tumours. The dose required to achieve these effects is, however, rather large (100 to 300 mg/kg weight). For this reason we have attempted to potentiate the effect of 6-azauridine by cancerostatics of other types. We have now found that the effect of 6-azauridine, as well as of 6-azacytidine[1], is markedly potentiated by 5-bis-(2-chloroethyl)aminomethyluracil (bis-chloroethylaminothymine, BCEAT), a cytostatic agent recently synthesised in these Laboratories[2].

Results of our experiments on Ehrlich ascitic tumours are summarised in the Tables I and II. The tumours employed are practically insensitive to 6-azauridine. However, when applied in combination with BCEAT the survival time of the experimental animals is increased to as much as twice that of the untreated controls. The superior properties of BCEAT as compared with the widely employed trichloroethylamine hydrochloride (TS-160 Spofa) are clearly evident from Table II. In the case of solid Ehrlich tumours (Table III) potentiation by means of BCEAT appears to be statistically significant in the case of 6-azacytidine but not in the case of 6-azauridine.

Zusammenfassung. Es wird gezeigt, dass die cancerostatische Wirkung von 6-Azauracil und 6-Azacytidin bei Mäusen durch 5-Bis-(2-chloroethyl)aminomethyluracil signifikant potenziert wird.

Tab. I. Ehrlich tumour (ascitic form). 20×10^6 cells were given i.p., therapy initiated on the day following inoculation, the drugs administered daily i.p. in physiological solution.

	Daily dose mg/kg	Total number of doses	Average survival time	Number of mice
Controls	–	–	12.5	12
Azauridine	250	8	13.3	12
BCEAT[a]	0.25	13	18.3	12
BCEAT and[a] Azauridine	0.25 250	14 14	26.0	11

[a] $P < 0.001$

Tab. II. Ehrlich tumour (ascitic form). 15×10^6 cells i.p., therapy initiated on the day following inoculation, the drugs given daily i.p. in physiological solution.

	Daily dose mg/kg	Total number of doses	Average survival time	Number of mice
Controls	–	–	12.9	13
BCEAT[a]	0.25	14	17.8	10
Trichloroethylamine hydrochloride	0.20[c]	11[d]	13.6	10
Trichloroethylamine[b] hydrochloride and azauridine	0.20 500	11[d] 11	16.8	10
BCEAT and[a] azauridine	0.25 500	14 14	23.2	9

[a] $P < 0.001$. [b] $P < 0.02$. [c] Equimolar with BCEAT. [d] The number of doses could not be increased; the animals began to die on the 11th day.

Tab. III. Ehrlich tumour (solid form). 20×10^6 cells were transplanted s.c., therapy initiated on the fourth day following inoculation, the drugs administered daily i.p. in physiological solution. The mice were killed on the 15th day following transplantation, weighed and the average weight of the tumours for each group determined.

	Daily dose mg/kg	Total number of doses	Average weight of tumour	Average weight of mice on the 15th day after transplantation	Number of mice
Controls	–	–	379	29.4	11
Azacytidine	250	9	345	27.1	10
Azacytidine[a] and BCEAT	250 0.25	9 9	261	24.4	10

[a] $P < 0.05$

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Gonadotrope Wirkung von Spermaextrakten

Nukaryia[1] zeigte, dass durch Spermainjektionen Kastrationsfolgen bei ♂ Ratten teilweise aufgehoben werden können. Fulconis und Chiapponi[2] sowie Vargas[3] zeigten, dass Spermainjektionen die Reifung der Follikel herbeiführen und dass die Veränderungen am Ovar jenen nach Gonadotropinverabreichung gleichen. In einer früheren Arbeit (Churý[4]) konnten wir die oben erwähnten Befunde bestätigen und ferner zeigen, dass auch resorbiertes Sperma ähnlich wirkt. Alle diese Befunde führten uns zur Annahme, dass bestimmte Sperma-Stoffe für die erwähnten Veränderungen verantwortlich sind. Die folgenden Versuche dienten deren Ermittlung.

Als Versuchsmaterial benutzten wir infantile Ratten und Mäuseweibchen, die in 9 Gruppen geteilt wurden (siehe Tabelle).

Gruppe	Zahl der Tiere	Versuchsdaten und Bemerkungen
I	11	Ratten, Spermaextrakt, ges. Menge 2,4 ml
II	8	Ratten, Spermaextrakt, ges. Menge 3,6 ml
III	7	Ratten, Spermaextrakt, inaktiviert, 2,4 ml
IV	15	Ratten, Azetonpräzipitatlösung 2,0 ml
V	17	Mäuse, Spermaextrakt, ges. Menge 1,2 ml
VI	13	Mäuse, Azetonpräzipitatlösung 0,8 ml
VII	9	Ratten, Kontrolltiere, Physiol. Lösung
VIII	10	Mäuse, Kontrolltiere, Physiol. Lösung
IX	10	Ratten, FSH, Kontrolltiere, ges. Menge 0,5–1,0 R.E.

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