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Does Color of an Antitumor Agent Predict for Clinical Antitumor Activity?

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Introduction

A number of investigators performing phase I trials have felt that compounds which are colored have a greater chance of showing clinical antitumor activity than those which are clear or white. To determine whether this was a definite phenomenon, we decided to investigate the question: Are colored compounds more likely to be clinically active than white or clear compounds?

Materials and Methods

Seventy-one compounds which are or have been undergoing clinical trials were utilized as a data base. Most of these compounds plus their colors are listed elsewhere [1, 2]. The compounds studied are listed in Tables 1 and 2.

To be considered active clinically, the compound had to exhibit good clinical antitumor activity ($\geq 25\%$ response rate) in any tumor type. The incidence of activity for colored compounds versus the activity of white or clear compounds was tested by the χ^2-method.

Table 1. Colored anticancer agents

Compound	NSC no.	Color	Proven clinical effectiveness
Methotrexate	740	Yellow	Yes
Actinomycin D	3 053	Yellow	Yes
Mithramycin	24 559	Yellow	Yes
Mitomycin C	26 980	Purple	Yes
Dichloromethotrexate	29 630	Yellow	Yes
Streptonigrin	45 383	Brown-black	No
2-3-Dihydro-IH-imidazo-(1,2-b)-pyrazole	51 143	Faint-yellow	Unknown
Chromomycin A_3	58 514	Yellow	No
CCNU	79 037	Slight yellow	Yes
Daunorubicin	83 151	Red	Yes
Streptozotocin	85 998	Cream	Yes
Methyl CCNU	95 441	Yellow	Yes
Camptothecin	100 880	Yellow	No
VM-26	122 819	Light yellow	Yes
Adriamycin	123 127	Red	Yes
Dichloroallyl Lawsone	126 771	Red	Unknown
Indicine-N-oxide	132 319	Yellow	Unknown
Rubidazone	164 001	Red	Yes
Chlorozotocin	178 548	Yellow	Unknown
m-AMSA	249 992	Orange-red	Yes
Dihydroxyanthracenedione	301 739	Blue	Unknown

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Table 2. White or clear anticancer agents

Compound	NSC no.	Proven clinically efficacy
Thioguanine	752	Yes
6 Mercaptopurine	755	Yes
Cycloleucine	1 026	No
2-Amino-1,3,4-thiadiazole	4 708	No
DON	7 365	No
Melphalan	8 806	Yes
Hexamethylmelamine	13 875	Yes
Gallium nitrate	15 203	No
5-Fluorouracil	19 893	Yes
Thymidine	21 548	No
Cyclophosphamide	26 271	Yes
Hydroxyurea	32 065	Yes
Methylglyoxol bis(guanyhydrazone)	32 946	Yes
TMCA	36 354	No
Vinblastine	49 842	Yes
Cytosine arabinoside	63 878	Yes
Vincristine	67 574	Yes
Thalicarprine	68 075	No
Trifluorothymidine	75 520	No
PCNU	95 466	Unknown
Yoshi 864	102 627	No
5-Azacytidine	102 816	Yes
Dibromodulcitol	104 800	No
Cytembena	104 801	No
L-Asparaginase	109 829	Yes
Ifosphamide	109 724	Yes
Pentamethylmelamine	118 742	Unknown
Diglycoaldehyde	118 994	Unknown
Cis-platinum	119 875	Yes
Bleomycin	125 066	Yes
3-Deazaurdine	126 849	Unknown
ICRF-159	129 943	Yes
1,2:5,6-Dianhydrogalactitol	132 313	No
2,5-Piperazinedione 3,6-bis-(5-chloro-2-piperidyl)-dihydrochloride	135 750	Yes
Baker's Antifol	139 105	No
Anguidine	141 537	No
VP16	141 540	Yes
Pyrazofurin	143 095	No
Cyclocytidine	145 668	No
Ftorafur	148 958	No
L-Alanosine	153 353	Unknown
Maytansine	153 859	No
Zinostatin (neocarzinostatin)	157 365	No
Acivicin (AT125)	163 501	Unknown
Bruceantin	165 563	Unknown
ICRF-187	169 780	Unknown
AZQ	182 986	Unknown
2-Deoxycoformycin	218 321	Unknown
PALA	224 131	No
BCNU	409 962	Yes

Results

As noted in Table 1, a total of 21 colored compounds have been brought into clinical trial over the past 12 years. In the case of five there is not enough clinical information available to assess their efficacy. Of the remaining 16 compounds, 13 (or 81%) have demonstrated clinical antitumor activity. As detailed in Table 2, 50 white or clear compounds have been brought to clinical trial over the same time period. Insufficient clinical information is available to assess the efficacy of ten of these. Of the remaining 40 compounds, only 20 (or 50%) have demonstrated some antitumor activity in phase II clinical trials. Therefore, the colored compounds have a statistically higher chance of being active in clinical trials than white or clear compounds ($P = 0.03$).

Discussion

The major purpose of this exercise was to try to validate or invalidate the clinical impression that a colored compound which is being studied in a phase I trial has a higher chance of being active in phase II clinical trials than a compound which is white or clear. The present study has shown that colored compounds do indeed have a higher chance of being clinically active. The implications of these findings are not entirely clear. However, it may point to a general principle that chromophores (particularly azo and *p* quinoid) are desirable in a new antitumor agent. Review of the preclinical activities of the azo (e.g., methyl red), triphenylmethane (e.g., crystal violet, phthalein (e.g., phenophthalein), and anthraquinoid (e.g., Alizarin) dyes might offer some new leads for colored compounds with usefulness in clinical practice.

References

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