Exploitation of Platinum for Human Solid Tumors*

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Abstract

As a single agent Pt has good clinical effectiveness in osteogenic sarcoma, as well as in ovarian cancer in the range of 50% as overall response rate, with lower rates (20%) in oesophageal cancer, cervix, head and neck, and germ cell tumors. Most of the reports have dealt with small series, often biased by pretreatment.

Combinations with alkylators, antimetabolites and antibiotics have frequently given higher response rates and even cures: especially in germ cell tumors (PVB regimen), osteogenic sarcoma (BMP), ovarian cancer (CP; CAP). The Pt + 5-fluorouracil combination yielded high response rates but was unable to produce cures in epidermoid tumors of the head and neck and oesophagus, as well as in ovarian and colonic adenocarcinomas. Combinations with methotrexate and bleomycin proved effective in epidermoid carcinomas of the head and neck and of the uterine cervix, while velban or vindesine or etoposide may reach (with Pt) 40% response rates in lung cancer.

In many of the examples cited above the response rate of the combination is higher than the sum of the response rates shown for the optimal use of the components as single agents: reasonably true synergism between Pt and bleomycin, velban, fluorouracil and methotrexate may be suggested. *In vitro* synergism has been documented between Pt and cytarabine, but only at dose levels non-compatible with intravenous injection: this combination however has been used intraperitoneally.

The literature is full of reports of combinations including Pt, used also in tumors where the response rate to Pt alone is far from defined. A rationale from *in vitro* preliminary studies capable of suggesting the optimal timing and optimal proportions among the different drugs is highly desirable and may lead to improved efficacy and lessened toxicity.

Introduction

Synergism, unlike additivity, is frequently defined as the condition where 1 + 1 equals more than 2. This definition is adequate for toxic as well as for therapeutic synergism and applies also to *in vitro* studies. A little more complicated is the concept of clinical or therapeutic synergism, where a balance is necessary for therapeutic and toxic interactions. In a practical situation, simple additivity of benefits without the same additivity in side effects is a clear therapeutic advantage, probably more acceptable than true synergism of therapeutic actions, accompanied by summation or synergism of the toxic effects. In this case the therapeutic index is indeed increased, and to term this 'synergism' may be incorrect, but operationally useful.

Sometimes, even the summation of 'different' side effects (e.g., giving moderate alopecia from drug A + moderate leucopenia from drug B) may well be acceptable, compared with potentiation of one side effect (e.g., when moderate leukopenia caused by drug C or by drug D may result in definitive agranulocytosis from the combination of drugs C and D).

From a clinical point of view we will compare some regimens of simple drugs in specific tumors with some regimens associating platinum with other drugs. The prerequisite will be that general cumulative toxicity of each regimen remains within ethical and psychological acceptability and we will confine ourselves to comparing the results in terms of complete remission rate (CR) and partial remission rate (PR) often looking to the overall remission rate (OR) that corresponds to CR + PR and, when appropriate, we will make reference to the duration of such remissions, or to the cure of some special groups of patients.

Stability of Pt in the presence of Cl^- ions in blood is a prerequisite for entering the cells, where the molecule may crosslink with 2 DNA bases, according to intra- or interstrand modalities, more easily in rapidly dividing cells. These facts were discovered after the discovery of antibacterial [1] and *in vitro* cytotoxic [2] activity. Many experimental tumors are sensitive to Pt [3]. Methotrexate and daunorubicin may suggest *in vitro* synergism with Pt, and their combination proves effective on alkylator-resistant clones. Etoposide has also shown synergism in laboratory animals [4, 5].

Results and Discussion

Synergism with radiation has recently been shown especially in cell cultures [6] with repair inhibition

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TABLE I. Effective Combinations in HN Tumours

Regimen	No. Patients	OR (%)	References
Pt + bleomycin	28	11	33
Pt + adriamycin	10	50	34
Pt + methotrexate	20	60	35
Pt + methotrexate + bleomycin	37	51	36
Pt + methotrexate + bleomycin	11	55	37
Pt + bleomycin + methotrexate	19	75	38
Pt + bleomycin + vincristine + methotrexate	22	27	39
Pt + vincristine + bleomycin	10	50	40

of DNA damage. Myelotoxicity is usually limited; emesis is only prominent in the first days of every course [7], while neurotoxicity (with hearing loss for frequencies above 4000 Hz) may emerge, usually in the long run.

The dose-limiting factor (nephrotoxicity) heralded by loss of magnesium-retention capability [8, 9] by the tubules (possibly leading to hypomagnesemic tetany) may be limited by (a) dose fractionation, (b) hydration, and (c) administration of 3% NaCl. The combination of these procedures allowed doubling of the maximum tolerated dose, and under these conditions the main toxic effects were shifted from nephrotoxicity to neurotoxicity and myelosuppression [10].

For lung cancer, the small-cell type has a response rate to Pt alone ranging from 0% [11] to 9 or 12% [12, 13].

According to preclinical studies cited above, Evans [14] administered Pt + VP + low dose radiation to the primary in 28 evaluable patients with an 86% OR rate (43% CR), while Murray alternated the Pt + etoposide (VP) regimen with CAV (cyclophosphamide, doxorubicin and vincristine) and obtained 94% OR; 70% were complete responders among 67 patients [15] with a projected 2-year survival rate of 35%. Clinical synergism is at least suggested.

In non-small-cell cancer of the lung (NSCCL) with Pt alone, on 38 patients there have been only 3 responses (approx. 8%) [11, 15, 16]. It is known that vindesine (VD) alone [23] may show some activity ranging from 20% of patients to 8% [17] but the combination of Pt + VD has increased the response rate from 23 to 53% [17, 18]. If the more optimistic data such as ours are to be believed, the term synergism may also be appropriate for NSCCL, on the basis of response rates obtained; but the best regimens are followed only by an increased survival of 'responders', not by an increased overall survival of the 'treated patients'.

For head and neck (epidermoid) cancers the potential of chemotherapy was very low before the introduction of Pt-containing combinations: methotrexate [24] and bleomycin [24] were among the most active single agents, obtaining short-lived responses in approximately 20% of patients, while 5-fluorouracil (Fu) was barely half as effective. Pt alone matched these results at low doses and gave around 30% at higher doses (Table I).

Several combinations of Pt with methotrexate, bleomycin, adriamycin and vincristine (Table I) brought the response rate to around 60% (average of several reports).

The combination of Pt and Fu (where 'expected' additivity is around 40%) has been found by Decker [25] to give consistently 94% overall and 63 complete remissions, and in non-pretreated patients 84 and 27% in our group [26]. In this case true synergism is strongly suggested.

In oesophageal cancer no single drug has consistently given a response rate over 15%, including Pt, Fu, bleomycin, doxorubicin and vindesine.

The first two drugs of this list (Pt + Fu) when combined may obtain up to 80% responses in small series of patients with non-metastatic tumors [27].

In advanced disease the response rate ranges between 33 and 50% according to various reports [28–31]. Here also synergism more than simple additivity is strongly suggested.

In testicular cancer the combination of Pt with bleomycin + velban or etoposide may cure around 70% of patients. The other drugs of the combination are effective in 10 to 20% of patients when used alone, or combined without Pt. On the activity of Pt alone there has been only one report [32] with 11 cases (8 OR) and this prevents a formal declaration of clinical synergism.

Discussion

At least for some tumors and with some agents platinum behaves synergistically. Suggestions have come sometimes from experimental studies (doxorubicin, methotrexate, etoposide and Ara Cγ) but in some cases the clinical results have anticipated the basic research, such as the combination of platinum + vindesine in NSCCL; Fu + cisplatin in oesophageal

and head and neck tumors. Models similar to this clinical situation could be constructed with transplanted and/or cultured tumors.

The aim of reverting from the clinical to the experimental study can be to optimize the combinations in terms of chronology and dose. Only on small animals or on *in vitro* cultures it is conceivable to conduct a series of tests were Pt and the proposed synergistic agents can be administered either concomitantly or in different sequences; after having established the optimal sequence, the minimum effective doses could be found, as well as the optimal proportions between two or more agents. From these data a new effort to increase the clinical therapeutic index may be started.

References

1 B. Rosenberg, L. VanCamp and T. Krigas, *Nature (London), 205,* 698 (1965).
2 B. Rosenberg, L. VanCamp, J. Trosko and V. H. Mansour, *Nature (London), 222,* 385 (1969).
3 C. W. Welsch, *Proc. Am. Assoc. Cancer Res., 12,* 25 (1971).
4 F. M. Schabel, Jr., M. W. Trader and W. R. Laster, Jr., *Cancer Treat. Rep., 63,* 1459 (1979).
5 J. H. Burchenal, L. Lokys and J. Turkevich, in A. W. Prestayko, S. T. Crooke and S. K. Carter (eds.), 'Cisplatin: Current Status and New Developments', Academic Press, Orlando, Fla., 1980, pp. 113–123.
6 E. B. Douple and R. C. Richmond, *Br. J. Cancer, 37,* (3), 98 (1978).
7 M. G. Kris, R. J. Gralla, R. A. Clark, L. B. Tyson, J. P. O'Connel, M. S. Wertheim and D. P. Kelsen, *J. Clin. Oncol., 3,* 1379 (1985).
8 O. Daniele, A. Fornasiero, E. Ferrazzi, V. Fosser and M. V. Fiorentino, in 'VII Corso di Aggiornamento in Oncologia Medica', Vol. II, Padova Deltagraph, Padua, Sept. 29–Oct. 4, 1980, pp. 789–796.
9 M. Rozencweig, D. D. Van Hoff, M. Slovic and F. M. Muggia, *Ann. Intern. Med., 86,* 803 (1977).
10 R. F. Ozols, B. J. Corden, J. Jacob, M. N. Wesley, J. Oschega and R. C. Young, *Ann. Intern. Med., 100,* 19 (1984).
11 A. H. Rossof, J. D. Bearden and C. A. Coltman, Jr., *Cancer Treat. Rep., 60,* 1679 (1976).
12 P. Dombernowsky, S. Sorenson and J. Aisner, *Cancer Treat. Rep., 63,* 543 (1979).
13 R. M. Levenson, Jr., D. C. Ihde and M. S. Huberman, *Cancer Treat. Rep., 65,* 905 (1981).
14 W. K. Evans, F. A. Shepherd and R. Feld, *J. Clin. Oncol., 3,* 1471 (1985).
15 N. Murray and E. Hodric, *Proc. Am. Soc. Clin. Oncol., 3,* 2149 (1984).
16 J. C. Britell, R. T. Eagan, J. N. Ingle, F. T. Creagan, J. Ruban and S. Frytak, *Cancer Treat. Rep., 62,* 1207 (1978).
17 E. Longeval and J. Klastersky, *Cancer, 50,* 2751 (1982).
18 M. V. Fiorentino, A. Paccagnella, L. Salvagno, V. Chiarion-Sileni, A. Brandes, O. Vinante, L. Endrizzi, S. Bolzonella and V. Fosser, *Fourth International Symposium on Platinum Coordination Complexes in Cancer Chemotherapy,* Burlington, June 22–24, 1983.
19 K. Kolaric, D. Vukas, A. Roth, V. Potrebica, J. Cervek and O. Cerar, *Tumori, 71,* 159 (1985).
20 K. Kolaric and D. Vukas, *Proc. ASCO, 5* (3) (1986).
21 S. M. L. Aversa, A. Fornasiero, O. Daniele, C. Ghiotto, P. Morandi and M. V. Fiorentino, *Tumori,* 686 (1986).
22 H. Yap, P. Salem, G. N. Hortobagyl, J. P. Bodey, A. U. Buzdar, C. K. Tashima and G. R. Blumenschein, *Cancer Treat. Rep., 62,* 405 (1978).
23 R. J. Gralla, E. S. Casper and D. P. Kelson, *Ann. Intern. Med., 95,* 414 (1981).
24 J. R. Bertino, M. B. Mosher and R. C. De Conti, *Cancer, 31,* 1141 (1973).
25 D. A. Dacker, A. D. Drelichman, J. Jacobs, J. Hoschuer, J. Kinzie, J. J. K. Loh, A. Weaver and M. All-Sarraf, *Cancer, 51,* 1353 (1983).
26 A. Paccagnella, P. L. Zorat, G. Cavaniglia, V. Chiarion Sileni, L. Faggionato, L. Tomio, D. Maretto, C. Marchiori and M. V. Fiorentino, *2nd European Conference on Clinical Oncology and Cancer Nursing (ABS),* Amsterdam, November 2–5, 1983.
27 S. Hallerstein, S. Rosen and M. Kies, *Proc. ASCO,* C-497 (1983).
28 J. Kish, A. Drelichman and J. Jacobs, *Cancer Treat. Rep., 66,* 471 (1982).
29 C. Gisselbrecht, F. Calvo and L. Mignot, *Cancer, 52,* 974 (1983).
30 A. Forestiere, H. Patel and J. Hanchins, *Proc. ASCO, 2,* 123 (1983).
31 D. P. Kelsen, C. Coonley and M. Bains, *Proc. ASCO, 2,* 128 (1983).
32 D. J. Higby, H. J. Wallace, Jr., D. J. Albert and J. F. Holland, *Cancer, 33,* 1219 (1974).
33 R. E. Wittes, F. Brescia, C. W. Young, G. B. Magill, R. B. Golbey and I. H. Krakoff, *Oncology, 32,* 202 (1975).
34 P. D. Bonomi, J. Mladineo, G. D. Wilbanks and R. Slayton, *Proc. Am. Assoc. Cancer Res. Am. Soc. Clin. Oncol., 18,* 311 (1977).
35 S. W. Pittman and D. R. Minor, *Proc. Am. Assoc. Cancer Res. ASCO, 20,* 419 (1979).
36 S. E. Vogl and B. H. Kaplan, *Cancer, 44,* 26 (1979).
37 E. G. Elias, P. B. Chretien and E. Monnard, *Cancer, 43,* 1025 (1979).
38 R. Caradonna, W. Paladino, J. C. Ruckleschel, J. C. Goldstein, J. E. Olson, J. W. Jaski, S. A. Silvers, S. Hillinger and J. Horton, *Cancer Treat. Rep., 63,* 489 (1979).
39 M. H. Amer, R. Izbicki and M. Al-Sarraf, *Proc. Am. Assoc. Cancer Res. Am. Soc. Clin. Oncol., 19,* 312 (1978).
40 L. Baker and M. Al-Sarraf, *Proc. Am. Assoc. Cancer Res. Am. Soc. Clin. Oncol., 19,* 312 (1978).