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Meeting Summary

NCI-EORTC Symposium on New Drugs in Cancer Therapy

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An NCI-EORTC Symposium on New Drugs in Cancer Therapy was held at the Institut Jules Bordet in Brussels on September 7–8, 1978. The purpose of the meeting was to review new drugs under clinical evaluation, with special emphasis on new anthracyclines. It was hoped that there would also be discussion and interaction on the methodology of the clinical evaluation of new drugs. The meeting was well attended and is another example of the close working relationship that has been established over the years between investigators in the United States and Europe. The meeting was given a truly international flavor by the participation of a major Japanese investigator.

Prof. Henri Tagnon opened the meeting, emphasizing the importance of a European rather than a national approach to oncology as part of the overall international battle against cancer. The first scientific paper was by Dr. Abraham Goldin, who spoke on the topic of 'Selecting the Winner'. He described the new NCI screen, which involves a prescreen of P-388 leukemia, followed by a solid tumor-dominated panel including three heterotransplant models. He presented data on two old drugs of the glutamine antagonist class (DON and azotomycin), which had shown a striking effect in the three human tumor xenograft models and so were being reconsidered for clinical trial. He spoke about the importance of correlating the animal tumors and human data. He outlined a correlation approach of human tumor spectrum with mouse tumor spectrum using some common drugs such as cyclophosphamide, 5-FU, and adriamycin.

Dr. Franco Muggia discussed the problems and pitfalls in the clinical evaluation of new drugs. He described the new phase II panel of the NCI, replacing the older signal tumors. This panel includes breast, colon, lung, melanoma, lymphoma, and acute leukemia. All new drugs sponsored by NCI would be tested against the panel. He outlined three problem areas of phase II study, which he labeled tumor biology, statistics, and ethics. These involve the problems of when phase II studies can and should be performed within a given tumor type and what numbers are required to attempt a meaningful decision. The rapid movement of a new drug into combination studies as soon as some activity is observed creates great problems in confirming the true activity of the drug. This is compounded for analogues, where comparative activity rather than activity per se is essential in the analysis.

Maurice Staquet spoke about the statistical problems in the analysis of new drug trials. The false-negative is more damaging than the false-positive in phase II trials, since a negative trial is not repeated and therefore a potentially valuable drug is lost. A positive trial is repeated and so ultimately the true answer is obtained. Phase II trials are usually over-optimistic, and utilization of the "Rule of 14", as initially described by Gehan leads to a high false-positive rate. His presentation failed to touch on the biologic complexity of the problem, entailing features such as patient selection variables and criteria of response definition, with Prof. Georges Mathé making a strong statement along these lines.

The rest of the first day was taken up with presentations on new drugs under clinical study by the investigators present.

Anhydro-ara-5-fluourocytidine (AAFC). Bavgarolas of Oviedo described the studies of the early clinical trials group of the EORTC. This drug is an analogue of arabinosyl cytosine and the Japanese drug cyclocytidine. Alberto of Geneva, in early trials with AAFC, had seen activity in upper gastrointestinal cancer, especially stomach. This was confirmed by the early clinical trials group, which observed a response rate in excess of 50% in upper gastrointestinal cancer. Some activity was also observed in head and neck cancer, but little in lung or breast. On a weekly schedule this drug does appear to offer a new building block for combination studies in stomach and pancreatic cancer. Alberto reported pilot

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data on the combination of AAFC + methyl CCNU, which did not appear encouraging.

Dr. F. Cavalli presented the EORTC early clinical trials group studies with *dianhydrogalactitol (DAG).* This Hungarian drug is an analogue, and supposed active metabolite, of dibromodulcitol. The studies in head and neck, lung, stomach, colon, and breast were all disappointing, with only a low level of activity. This drug appears to be a failure and it was reported that in Hungary they have gone back to using dibromodulcitol.

DeJager of Brussels presented the EORTC data on *DDMP,* the folate antagonist. This drug has lower affinity for dihydrofolate reductase than methotrexate, but has transport characteristics that make it attractive conceptually. The EORTC has had great problems in working out a proper dose schedule with citrovorum factor (CF). DDMP administered PO on day 1 with CF either IM or IV on days 2–4 Q6H × 12 has been used at three dose levels to treat 130 patients. Responses in five of nine cases of head and neck cancer and four of five epidermoid lungs were reported at the lowest CF level. As the dose level of CF was increased the activity fell, as did the toxicity; and a true balance has still not been worked out. The drug is active, but is not easy to use, and the question of comparative effect with methotrexate still remains to be established.

Rozencweig of Brussels outlined the exciting activity of *cis-diamminedichloroplatinum,* and then Georges Mathé spoke on *malonato 1,2-diaminocyclohexane platinum.* This new analogue is now in phase I trial. Platelet toxicity and vomiting have been observed, but no renal toxicity as yet. According to Mathé, this drug may not be cross-resistant with the original *cis*-platinum.

Makoto Ogawa gave an outline of *new drugs under clinical study in Japan.* These included:

1. FD-1 } analogues of Ftorafur
2. HCFU }
3. N_4-Benhoyl-ara-C
4. A-145 or *N*-ethyloxycarbonylaminoethyl-L-Isoleucine
5. PEP-bleomycin
6. Ia-Linoleoyl mitomycin C
7. GANU }
8. MNCU } nitrosourea analogues
9. ACNU }
10. Neothramycin
11. Aclacinomycin

Vindesine is a new vinca alkaloid developed with the hope of both improving on the neurotoxicity of vincristine and increasing the efficacy rate. Mathé reported high activity for vindesine in acute lymphocytic leukemia, blast crisis of CML and the non-Hodgkin's lymphomas. Smith of Sutton reported 6/23 responses in breast cancer and 2/14 in melanoma. The drug is limited by marrow toxicity and when total doses exceed 20 mg cumulative neurotoxicity is seen. The critical unanswered question is how vindesine compares with vincristine and vinblastine. Vincristine is neurotoxic but has the great advantage of low marrow toxicity. If you trade dose-limiting neurotoxicity for dose-limiting marrow toxicity you have vinblastine, which also lacks cross-resistance with vincristine. Marrow toxicity makes both vinblastine and vindesine less attractive for combination study than vincristine. The same problem of comparative interpretation exists for *formyl leurosine,* the Hungarian vinca, which in preliminary data reported by S. Kerpel-Fronius is, also marrow-toxic. A real challenge will be to develop a clinical test strategy for new vincas that allows meaningful comparison with *both* vincristine and vinblastine.

Blum of Boston detailed the phase I and II studies with *maytansine* at the Sydney Farber Cancer Institute. This natural product has gastrointestinal toxicity, neurotoxicity, and hepatic toxicity, along with mild myelosuppression and stomatitis. The formidable toxicologic spectrum of this drug is unfortunately matched with a low order of activity. The response rates in phase II include 1/33 in breast, 0/25 in colon, 0/17 in lung, 1/18 in melanoma, 0/10 in soft-tissue sarcoma, 1/9 in ovary, and 1/4 in bladder cancers.

Chlorozotocin is a nitrosourea analogue for which experimental data indicate lower myelosuppression with high activity. A phase I study by Schein at Georgetown established a low myelosuppressive dose of 120 mg/m^2 but did not establish a classic MTD. At 120 mg/m^2 he reported 4/24 responses in colon cancer and 4/20 in melanoma. Baker presented a phase II study from Wayne State with a dose of 120 mg/m^2, which was disappointing as no responses were seen in 16 breast cancer patients and 35 colon cancer patients. No cumulative myelosuppression was seen after four courses.

Mathé presented data on two sugar-linked nitrosoureas, *RFCNU and RPCNU,* which he compared with chlorozotocin as part of the USA-France Cancer Research Agreement. RPCNU has much higher alkylating activity than RFCNU and is immunosuppressive while the latter is not. Phase I studies with both drugs indicate RFCNU is less marrow-toxic, and it appears to be the choice for further study.

AMSA is 4′-(9-acridinylamino)methane-sulfon-*M*-anisidide and was chemically synthesized by Bruce Cain of New Zealand. It is active against a wide range of experimental tumors, and six phase I studies have been undertaken under the sponsorship of the NCI. Van Hoff of NCI presented a review of the interesting data to date. At NCI a single dose every 4 weeks has been used, and leukopenia is dose-limiting with occasional platelet suppression, phlebitis, and nausea and vomiting being observed. A response in ovarian cancer was reported. At M.D. Anderson Hospital, 3/12 AML patients, who

were heavily pretreated, have achieved CR at doses of 75 mg/m²/day for 5 days. In addition, a breast cancer response was seen. Responses have been observed in other phase I studies and this drug appears to be highly promising.

The current status of the highly touted and publicized *PALA* was discussed by Valdivieso of M.D. Anderson Hospital. In their phase I study doses have gone up to 3600 mg/m²/day for 2–3 days with no responses seen. While the drug is not myelosuppressive, severe skin rash and mucositis appear to be dose-limiting. In most patients studied, aspartate transcarbamylase levels have decreased, but without concomitant antitumor response. The data to date are disappointing, but it is still very early.

Mouridsen of Copenhagen outlined a study performed with *prednimustine (Leo 1021)* in breast cancer. This drug links chlorambucil and prednisone. Thirty-six patients with advanced breast cancer were treated with 40 mg/m²/day, 35 being evaluable. Responses were seen in 40% (14/35), with two CR and 12 PR. The median duration of response was 5 months (range 3–9+). In 28 patients with prior chemotherapy (including cyclophosphamide-containing combinations) responses were seen in 10. Marrow toxicity was significant and dose-limiting. This drug appears to be active in advanced breast cancer, and deserves further study.

Bonadonna presented a study of high-dose *medroxyprogesterone acetate* in advanced breast cancer. Doses used were 1500 mg/day (28 patients) and 1000 mg/day (53 patients). All patients were resistant to chemotherapy and 37% also to endocrine therapy. Responses were seen in 6/21 at the high dose, and 17/53 (32%) at the low dose, giving an overall response rate of 28%. The median duration of response was 6 months and median survival 13.5 months, responders having a median survival of 2+ years. Toxicity was mild, consisting of weight gain, gluteal abscesses, and muscle cramping.

Paoletti reviewed the current status of various *ellipticine derivatives,* with *9-OH ellipticine* appearing to have some promise. Lowenbraun ended the day with a negative phase II study of the southeastern group on *anguidne* in solid tumors.

The second day was devoted entirely to an overview of current anthracyclines and will be published in Cancer Treatment Reports. No attempt will be made to summarize the excellent overviews given by people such as Schwartz, Bachur, Phillips, Davis, Von Hoff, Praga, Daniels, Casazza, Henry, and Myers. A significant time was spent reviewing the current clinical status of eight analogues under study.

1. Adriamycin and daunomycin DNA complex. Trouet reviewed 600 patients treated to date in Belgium with these DNA complexes. Three controlled trials have been done. In childhood ALL adriamycin-DNA was superior to daunomycin-DNA. In AML no difference was observed between daunomycin + Ara-C and daunomycin-DNA + Ara-C. In anaplastic lung cancer adriamycin alone followed by adriamycin-DNA was superior to adriamycin-DNA alone. No cardiac toxicity has been observed. It takes 4 h to infuse a dose of the DNA complex.

2. Diethoxy-1-acetoxy-14-daunorubicin. This Rhone-Poulenc analogue has been studied by the group of Jean Bernard and was reported on by Jacquillat. One hundred nine patients have been treated and high response rates seen in acute lymphocytic leukemia and non-Hodgkin's lymphoma. The lymphoma group had mainly failed on CHOP, and so Jacquillat had the impression that this analogue might lack cross-resistance with adriamycin. Responses have been seen in 5/6 mycosis fungoides patients. The EORTC has seen solid tumor activity in breast, cervix, lung, and melanoma, but no figures were given. Marrow toxicity is dose-limiting and diarrhea can be significant. No cardiac toxicity has so far been seen. This drug, called 14 DEA daunorubicin, appears highly active and worth further study. It appears to have replaced rubidazone as the high-priority analogue of Rhone-Poulenc.

3. Quelamycin. This an iron-containing adriamycin complex developed and studied in Spain. Cortes-Funes presented phase I data indicating systemic reactions due to the iron in the complex, including fever, chills, and dyspnea. This has been controlled to some degree and a 7/37 response in mixed tumors was reported.

4. 4'-EPI adriamycin. Bonadonna has reached 90/mg/m² every 3 weeks in phase I study with this new Farmitalia analogue. At this dose only minimal myelosuppression has been observed and the MTD is not yet reached. This drug has the same molecular weight as adriamycin and differs only in an isomeric change in the sugar. The lack of significant marrow toxicity at 90 mg/m² is encouraging.

5. Carminomycin. This Soviet Union analogue of daunorubicin discovered by Gause has just begun phase I study in the United States under the sponsorship of the Bristol Company. Baker at Wayne State is using the drug orally and has reached 36 mg/m² as a single dose without any toxicity. Using a single IV dose schedule, Comis at Syracuse has seen myelosuppression at the 15 mg/m² level.

6. AD-32. The phase I study in Boston was reported on by Blum. Twenty-three patients have received 74 courses of the drug, given as single doses every 3 weeks.

Doses as high as 700 mg/m^2 have been administered with 600 mg/m^2 every 3 weeks reported as the MTD. Because of its low solubility, the drug is formulated in an emulphor vehicle and must be infused over 24 h. Systemic reactions from the emulphor have been observed and are controlled by IV cortisone, which is now given routinely with each course. Marrow suppression is dose-limiting, nausea rare, alopecia mild, and there has been no evidence of mucositis or ulceration upon extravasation.

7. Rubidazone. Benjamin reviewed the extensive United States data with this daunomycin Rhone-Poulenc analogue. The drug is clearly active in adult acute leukemia, but its superiority to either adriamycin or daunomycin is not established. It is clearly inactive in solid tumors, according to studies at the M.D. Anderson and Wayne State Hospitals. The drug is cardiotoxic, as shown by the development of cardiomyopathy, and so does not appear to be a dramatic inprovement in this area.

8. Aclacinomycin-A. This compound, discovered by Umezawa, has three sugars and is related to cinerubin. It is notable for being negative in the Ames test and less cardiotoxic in a hamster model. Phase I trial in Japan indicated that marrow toxicity is dose-limiting, with nausea and vomiting being significant. Mucositis and alopecia are minimal, but liver toxicity has been observed. In phase II study solid tumor activity is seen, but it is too early to say anything about cardiac toxicity.

The anthracycline meeting presented an international buffet on new analogues, with dishes from Belgium, France, Italy, Spain, Russia, the United States, and Japan. As with any buffet, there is a tendency to eat too much by intake of small amounts from many dishes. The same could be said of the meeting. At the end the audience was satiated but probably wanted and needed to know more about the compounds described. This would have included details on rationale for clinical trial, such as the critical decision-making experiments and strategy for clinical evaluation. What appears to be lacking with these drugs is a meaningful plan for phase II and III studies, with the end-point of a decision about whether the new analogue has an improved therapeutic index compared with adriamycin. The distinct danger exists that thousands of patients will be treated with these analogues and no clear decision will be possible. It would be tragic to repeat the nitrosourea story, where new analogues continually enter clinical trial but the old analogues are still around and no clear superiority can be established for one over the other.

A plethora of analogues does offer one significant potential. It offers the possibility of correlative analysis of the experimental data and the clinical predictiveness. If a correlative analysis with ten drugs were made it would presumably be possible to determine which test systems seem valuable and which do not. This will only be possible if some coordination of clinical strategy is achieved, with agreement on coining some definitions and data-reporting requirements. Not to attempt to do this would be to miss an important opportunity.

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