34th annual meeting of the american society of oncology (ASCO) Los Angeles, California, USA, 16-19 May 1998

de Vries, Elisabeth G.E.; Kaye, Stan B.

Published in:
Drug Resistance Updates

DOI:
10.1016/S1368-7646(98)80009-5

Publication date:
1998

34th Annual Meeting of the American Society of Oncology (ASCO)

Los Angeles, California, USA, 16–19 May 1998

Elisabeth G.E. de Vries,[1] Stan B. Kaye[2]

[1]Department of Medical Oncology, University Hospital Groningen, The Netherlands [2]CRC Department of Medical Oncology, Beatson Oncology Centre, Glasgow, UK

This international conference attracted over 18 000 attendees. ASCO's president Robert J. Mayer noted in his opening comments that almost half of the 2300 abstracts presented were from countries other than the USA, which made it 'a truly world cancer congress'. Abstracts can be retrieved from the ASCO web site http://www.asco.org. The first 2 days were devoted to educational sessions, meet-the-professor sessions and tumor panels. Here we will summarize some presentations relevant to the field of drug resistance.

P-glycoprotein. Several studies examined the role of the drug efflux pump P-glycoprotein in cancer chemotherapy. Among them were studies analyzing the effect of combining chemotherapy with P-glycoprotein modulators, particularly the non-immunosuppressant cyclosporin analogue PSC833 (currently in phase II/III trials). Apart from effective P-glycoprotein blockade in vitro, PSC833 was found in earlier in vivo studies to alter the pharmacokinetics of chemotherapeutic drugs, allowing their lower dosage in combination treatment. Now data were presented (Advani, Stanford University, CA) for the effect of PSC833 in combination regimens that included paclitaxel. The maximum tolerated dose of doxorubicin (iv bolus) followed by paclitaxel (1 hour infusion) were 35 mg/m^2 and 150 mg/m^2, respectively. With PSC833 (5 mg/kg p.o., qid), administered for a total of 12 doses starting 1 day prior to chemotherapy, the maximum tolerated dose of doxorubicin dropped to 15 mg/m^2 and paclitaxel to 80 mg/m^2. Pharmacokinetic analyses of paclitaxel, doxorubicin and their metabolites indicated that PSC833 inhibits the disposition of the two drugs, thus accounting for the need to reduce the dose approximately 2-fold. Patnaik et al (University of Toronto, Canada) performed a phase I dose-finding and pharmacokinetic study of paclitaxel with carboplatin in combination with oral PSC833. In this study, the area under curve (AUC) for carboplatin without paclitaxel or PSC833 was as expected. In chemotherapy naive patients, they observed as maximum tolerated dose of carboplatin AUC 6 mg/ml.min, paclitaxel 81 mg/m^2 and PSC833 5 mg/kg orally qid for a total of 12 days. Planting et al (Rotterdam Cancer Institute) reported on a phase I pharmacokinetic study aiming at a 100 ng/ml plasma concentration of the P-glycoprotein inhibitor GF120918 with doxorubicin 50–75 mg/m^2 in patients with advanced solid tumors. Based on preclinical data, GF120918 was considered to be of interest because of low potential for pharmacokinetic interactions with cytotoxic agents such as doxorubicin. The toxicity of GF120918 alone was somnolence. It was concluded that this combination treatment did not require major reductions of doxorubicin, but that GF120918 increased doxorubicin levels in various patients. The dose-limiting toxicity of the combination was neutropenic fever. The recommended dose for this combination in future studies was doxorubicin 60 mg/m^2 day 3 plus GF120918 in a dose of 400 mg bid day 1–5, cycles every 3 weeks.

Schellens et al (Netherlands Cancer Institute, Amsterdam) proposed that the oral bioavailability for paclitaxel is probably low due to its high affinity for the P-glycoprotein pump. This pump is abundant in the gut. They showed that oral cyclosporin A strongly enhanced the bioavailability of orally administered paclitaxel in patients.

Rahman et al (MD Anderson Cancer Center, Houston TX) made a completely different use of the fact that *MDR1* gene overexpression may lead to cell insensitivity for chemotherapeutic drugs. They transfected bone-marrow stem cells of patients with breast and ovarian carcinoma with the *MDR1* gene. They hoped to prove the feasibility of this gene transfer technique and be able to increase paclitaxel dosage immediately post-transplant to affect complete response rates. Autologous CD34 + cells modified by retrovirus carrying *MDR1* cDNA could indeed be engrafted after high-dose chemotherapy. The modified cells were detectable in bone marrow, however, only at the time of the first course of paclitaxel and only in five out of 20 patients. Cytotoxic chemotherapy could be safely administered immediately upon recovery from autologous stem cell transplantation.

Alberts et al (Arizona Cancer Center, Tucson) reported that *MDR1* expression in ovarian carcinoma patients is an independent risk factor for poor survival in optimal stage III ovarian cancer. Until now, there was no clear consensus in the literature that *MDR1* expression plays a role in chemotherapy sensitivity in ovarian carcinoma. Alberts et al performed a study in 86 fresh ovarian cancer specimens obtained during initial laparotomy. Of the 86 patients, 69 had stage III disease. *MDR1* expression was measured as P-glycoprotein expression. immunohistochemically using the JSB-1 monoclonal antibody. Strongly positive expression was defined as all cells being strongly positive. In the subset of patients with stage III optimal disease, *MDR1* expression status was strongly associated with survival (p=0.006). Of the 45 patients with optimal stage after initial debulking surgery, nine had strongly positive staining cells and a median survival of 9.8 months, while six had faintly positive cells and a median survival of 32.6 months. The

survival for patients (n=11) with negative tumors has not yet been reached. Patients with suboptimal stage III (≥2 cm disease left after initial debulking) or stage IV ovarian cancer and elevated *MDR1* expression did not have poorer survival. The authors concluded that *MDR1* expression is more common than previously documented, namely 20% in stage III. They considered further studies with modulation therapy to overcome drug resistance worthwhile in *MDR1*-overexpressing stage III patients. It was not reported whether chemotherapeutic drugs affected by P-glycoprotein were used in the patients studied. Nevertheless, the findings are of interest since paclitaxel is a substrate for P-glycoprotein and is now a standard component of first-line chemotherapy for ovarian carcinoma.

Topoisomerase II. The two isozymes, topoisomerase IIa (topIIa) and IIb, are targets for drugs such as the anthracyclines and epipodophyllotoxins. Since topII b has only been recently discovered, few data are available on its role in drug resistance. Dingemans et al (Free University, Amsterdam) performed a study to evaluate the relationship between expression of drug resistance- and apoptosis-related markers with response to chemotherapy and survival in small cell lung carcinoma (SCLC) patients. Patients were selected from a phase III trial in which they were randomized to receive either cyclophosphamide/epirubicin/etoposide or cyclophosphamide/epirubicin/vincristine alternating with carboplatin/etoposide. Thus, both arms of the trial included the topIIb inhibitor epirubicin. Paraffin-embedded tumor sections were obtained prior to treatment from all 93 patients. Immunohistochemistry was performed using specific mouse monoclonal antibodies directed against topIIa, top IIb, p53, p21 and bcl-2 and the percentage of positive tumor cells was estimated. The score for topIIa and topIIb was divided into 3 groups (<30% (±), 30–60% (+) and >60% (++)) and for p53, p21 and bcl-2 into 2 groups (<10% (-) and >10% (+)). The difference in survival observed when selected for topIIa expression was most pronounced in the patients with limited disease ($p<0.0001$). Lower response rates were observed in patients with high topIIb expressing tumors (<0.05). Furthermore, high topIIa levels were predictive for shorter survival and patients with bcl-2 negative tumors had a higher 2-year survival rate. These data suggest a role for topIIa and topIIb in SCLC.

Tumor suppressor p53. There was great interest in the role of the tumor suppressor gene p53 in determining sensitivity of tumors to chemotherapeutic drugs. Katsaros et al (University of Turin, Italy) studied the prognostic and predictive value of p53 and WAF1 expression in 148 ovarian carcinomas. They observed that p53 protein accumulation detected by ELISA was a significant indication of increased risk for patient death but not for relapse. WAF1 expression was uninformative for prognosis. Another study of ovarian cancer, by Tropé et al (Norwegian Radium Hospital Oslo) assessed the predictive value of p53 status according to whether patients received paclitaxel or cyclophosphamide as part of platinum-combination therapy in a randomized trial. Interestingly, the presence of wild-type p53 did not differentiate between the two treatments, but for patients with p53 mutations there was a significantly better relapse-free survival ($p=0.002$) on the paclitaxel arm compared to the cyclophosphamide arm. This confirms other data which point to sensitivity to paclitaxel in p53-mutant cancer cells.

The fact that in animal models gene therapy with wild type p53 increased tumor sensitivity to chemotherapeutic drugs has stimulated similar clinical studies. All studies presented at this meeting were still at an early phase. Timmons et al (Introgen Therapeutics, Houston, TX) monitored vector dissemination and excretion in patients with non-SCLC treated with intratumoral injections of Ad-p53, a replication-defective adenoviral vector containing the wild-type p53 gene. In a dose-escalating phase I/II trial, 52 patients received up to six monthly injections; 24 of these patients also received cisplatin iv. The vector was present in the plasma within 30 minutes of injection, excreted in urine and sputum within 24 hours and cleared after 6–12 days. Intratumoral injections of Ad-p53 resulted in vector dissemination into body fluids in a dose-independent manner, despite the presence of anti-adenoviral antibodies.

Swisher et al (University of Texas MD Anderson Cancer Center), evaluated the safety and gene transfer efficiency of monthly intratumoral injections of Ad-p53 with or without cisplatin in 52 patients with advanced non-SCLC who failed conventional treatments. Ad-p53 doses were escalated and injected monthly into a single primary or metastatic tumor by bronchoscopy (n=7) or computed tomographic guidance (n=45). Of the patients who received Ad-p53 alone (26 evaluable), two experienced a partial response and 16 stable disease. Combination of Ad-53 and cisplatin (n=23) resulted in partial response in three and stable disease in 17.

Progression-free survival was 2–4 months for Ad-p53 alone and 6.2 months for the combination. These results suggest that adenoviral-mediated p53 gene transfer can be safely accomplished with or without cisplatin. An alternative approach is to target (resistant) tumour cells which have dysfunctional p53. This can be achieved with the attenuated adenovirus, Onyx-015, which bears an E1B-deletion and has been shown to selectively replicate in such cells. Kirn and co-workers (Beatson Oncology Center, Glasgow, Scotland) reported a Phase II trial of direct intratumoral injection of Onyx-015 in patients with advanced head and neck cancer, noting that four of 13 patients so far had shown tumour regression. He also reported preclinical data showing efficacy for Onyx-015 in a p53-deficient ovarian cancer cell line. An intraperitoneal Phase I trial of this approach is underway and, as with Ad-p53, the combination with standard chemotherapy is being studied further because of the potential for resistance circumvention.

New drugs. Numerous studies with new drugs were presented. The now established topoisomerase I inhibitor CPT-11 was compared with best supportive care in a randomized

study of patients with 5-FU resistant metastatic colorectal cancer (Cunningham, Manchester). It was found to increase pain-free survival, improve quality of life, and increase overall survival from 6.5 months to 9.2 months.

Finally, considerable publicity surrounded the report of the first randomized trial examining the potential of a humanised monoclonal antibody directed against the membrane receptor HER-2/neu (anti-HER-2/neu). Slamon and co-workers (UCLA School of Medicine, Los Angeles, CA) reported on a randomized trial of 469 patients with advanced breast cancer who received chemotherapy (doxorubicin/cyclophosphamide or paclitaxel) with or without weekly anti-HER-2/neu, iv. Preclinical data have indicated that anti-HER-2/neu prevents DNA repair after chemotherapy, and therefore has the potential to reverse drug resistance. The randomized trial showed a significant benefit for the addition of anti-HER-2/neu, with a response rate increase from 36 to 62% and a time to tumour progression increase from 5.5 to 8.6 months. Some (anthracycline-related) increase in cardiotoxicity was also seen, but this study raises hopes that selective inhibition of key intracellular signals can make a significant difference in the sensitivity of cancer cells to conventional chemotherapy.

Correspondence to: Elisabeth G.E. de Vries, MD, PhD, Department of Medical Oncology, University Hospital Groningen, PO Box 30.001 9700 RB Groningen, The Netherlands. Tel (31) 50 361 28 21, Fax (31) 50 361 4862, E-mail e.g.e.de.vires@int.azg.nl