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Promising new developments in cancer chemotherapy

Abstract The positive impact on survival of traditional chemotherapeutic agents has renewed interest in developing newer cytotoxic agents and orally active compounds with improved therapeutic indices. In addition, new insights into the pathways of human tumorigenesis have led to novel approaches aimed at specific mechanism-based targets. The taxane class, of which paclitaxel was the first member, has the unique ability to promote and stabilize microtubule function directly, thereby inhibiting mitotic progression and inducing apoptotic cell death. Paclitaxel provides treatment benefit in a broad range of solid tumors including breast, ovarian, and lung cancer. The success with paclitaxel stimulated interest in the microtubule as a new therapeutic target. Taxane analogues with improved preclinical efficacy have been identified and are entering clinical trials. The enthusiasm for oral anticancer agents and the therapeutic importance of platinum compounds has led to the development of JM216 (satraplatin), a novel platinum IV coordination complex with oral activity in cisplatin-resistant cell lines, which is now in phase III trials in prostate cancer. Another compound in late development is DPPE, a chemopotentiator that enhances the in vivo antitumor effects of cytotoxic agents such as doxorubicin, cyclophosphamide, and cisplatin. Agents that inhibit topoisomerase I and II have also been of interest. TAS-103 is a dual topoisomerase I and II inhibitor with preclinical efficacy in a broad spectrum of tumors and in multidrug-resistant tumor cell lines. Vaccination strategies represent a rational therapeutic approach in the minimal residual disease or high-risk adjuvant therapy setting. The GMK and MGV vaccines utilizing ganglioside antigens overexpressed on human tumors such as melanoma and small cell lung cancer appear to induce antibody production reliably at tolerable doses and are under further clinical investigation. Inhibition of matrix metalloproteinases (MMPs) is another attractive target for intervention in several aspects of tumor progression. Local production of MMPs with subsequent degradation of the extracellular matrix is implicated in supporting tumor growth, invasion, and angiogenesis. The development of orally active, nontoxic MMP inhibitors is critical since these compounds will likely require chronic administration in conjunction with other therapies. Oncogenes and tumor suppressor genes are appealing targets for therapy since they are thought to be responsible for a significant number of cancers. Mutations in the Ras oncogene occur with great frequency in a number of human cancers including lung, pancreas, and colon cancer. Clinical development of potent and selective inhibitors of farnesyltransferase, the Ras-processing enzyme, is ongoing. These compounds uncouple Ras activity, affect tumor growth, and have demonstrated significant antitumor activity against experimental models of human cancer. The exciting compounds and novel therapeutic approaches currently under investigation by Bristol-Myers Squibb Pharmaceutical Research Institute offer great potential as effective cancer chemotherapy agents for the near future.

Key words Cytotoxics · Taxanes · Vaccines · MMPI Ras-FTI

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Introduction

Traditional anticancer therapies have demonstrated the ability to prolong survival in the advanced disease set-

ting [35, 75, 78]. More importantly, they have influenced the primary therapy of cancer, where significant treatment benefits have been realized [5, 28, 62, 63, 66, 67]. The addition of chemotherapy to the treatment of patients with early-stage malignant disease improves the likelihood of long-term survival. Consequently, there has been a resurgence in interest in developing new cytotoxic agents, analogues, and orally active agents with altered or enhanced activity profiles. Additionally, recent research efforts have focused on novel mechanism-based approaches targeting pathways responsible for oncogenesis. This review discusses some of the innovative compounds under development by Bristol-Myers Squibb (BMS) Pharmaceutical Research Institute which offer promise for further substantial advancement in the successful treatment of human cancer.

Compounds in late development

Paclitaxel

The taxane class, of which paclitaxel was the first member, has the unique ability to promote and stabilize the assembly of tubulin into microtubules, the cellular structure that forms mitotic spindles and is required for chromosome segregation [20, 76]. In the presence of paclitaxel, cells accumulate in the mitotic phase of the cell cycle and undergo apoptosis as they attempt to divide. Paclitaxel is active and provides clinical benefit in a broad range of solid tumors including breast, ovarian, and lung cancer. Early clinical studies in advanced ovarian cancer demonstrated relevant antitumor activity and prolongation of time to progression in patients who had developed resistance to standard platinum-containing chemotherapy [24, 25, 49, 57, 84, 85]. Similarly, significant efficacy was observed with paclitaxel in breast cancer patients who had failed standard therapy, which included prior anthracyclines [1, 22, 65, 71]. The evidence for clinical non-cross-resistance between paclitaxel and the platinums or anthracyclines supported the evaluation of paclitaxel in combination with these important agents. Furthermore, it was logical to evaluate paclitaxel combination therapy in earlier stages of disease to maximize the potential beneficial impact of treatment.

In a randomized phase III trial conducted by the Gynecologic Oncology Group (GOG) in previously untreated patients with ovarian cancer, paclitaxel in combination with cisplatin resulted in significantly longer progression-free survival (median 18 vs 13 months, $P < 0.001$) and greater than one year longer median survival (median 38 vs 24 months, $P < 0.001$) compared with standard therapy with cyclophosphamide and cisplatin [58]. The results of the GOG-111 study have recently been confirmed by the European Organization for the Research and Treatment of Cancer (EORTC) Intergroup trial in advanced ovarian cancer: patients treated with the paclitaxel and cisplatin combination had a significant advantage in terms of progression-free survival as well as overall survival compared to the cyclophosphamide and cisplatin treatment group [79]. Recently, Cancer and Leukemia Group B (CALGB) reported planned interim results from the phase III Intergroup study (CALGB 9344) that may represent the most significant advance in the adjuvant treatment of breast cancer in many years. This trial demonstrated that the sequential addition of paclitaxel to standard adjuvant therapy with doxorubicin and cyclophosphamide significantly prolonged the duration of disease-free and overall survival in women with node-positive breast cancer [36]. In terms of proportional benefit, paclitaxel reduced the recurrence rate by 22% and the death rate by 26%.

In advanced non-small cell lung cancer (NSCLC), the efficacy of paclitaxel in combination with cisplatin has been confirmed in three large phase III randomized controlled trials. Studies conducted by the Eastern Cooperative Oncology Group (ECOG), the EORTC, and BMS demonstrated superior response rates, increased time to progression, symptom alleviation, and comparable survival when paclitaxel in combination with cisplatin was compared to a cisplatin-containing regimen [6, 30, 31]. The activity of paclitaxel in advanced NSCLC was further confirmed in a recently completed phase III randomized trial in which single-agent paclitaxel significantly prolonged survival compared to best supportive care [83]. The full scope of potential therapeutic benefits from paclitaxel treatment, alone and in combination therapy, has yet to be realized and remains an active area of clinical research. In addition to studies in early-stage breast, ovarian, and lung cancer, there are ongoing trials in a wide range of tumor types including head and neck, bladder, small cell lung, endometrial, and gastric cancer.

JM-216 (satraplatin)

There is a renewed interest in oral chemotherapy drugs, given their ease of administration and potential for cost containment. JM-216 (satraplatin) (bis-acetato-ammine-dichloro cyclohexylamine platinum IV) is the first platinum analogue to be active by the oral route. In vitro cytotoxicity testing with JM-216 demonstrated comparable activity to cisplatin against several human and murine tumor cell lines, while cell lines resistant or innately insensitive to cisplatin did not show complete cross-resistance [41, 43, 69]. Generally, in vivo antitumor activity was comparable to that of parenterally administered cisplatin or carboplatin. JM-216 was ineffective in the few in vivo tumor models tested that were insensitive or resistant to cisplatin [41, 59, 73]. Combination studies in mice confirmed that JM-216 and oral etoposide were therapeutically synergistic in the intravenous P388 leukemia model [41].

Clinical studies with JM-216 were initiated in 1992 and to date approximately 400 patients have been

treated in phase I and II trials. Studies exploring different dosing schedules have demonstrated that the dose-limiting toxicities are myelosuppression (thrombocytopenia and neutropenia) and diarrhea [41]. Hematologic toxicity has been cumulative, requiring dose reduction and treatment delay, whereas nephrotoxicity and neurotoxicity have been infrequently reported. The recommended phase II dose is 100–120 mg/m^2 daily for 5 consecutive days every 3–4 weeks. In addition, a daily dose of 30–40 mg/m^2 for 14 consecutive days every 5 weeks is being further explored in phase II trials.

To date, activity with JM-216 has been demonstrated in phase II studies in small cell lung cancer, relapsed ovarian cancer, and hormone-refractory prostate cancer. Recently, a phase III trial has been initiated by the EORTC comparing JM-216 plus prednisone to prednisone alone in patients with hormone-refractory prostate cancer. The primary study endpoints are survival and time to pain progression. A second double-blind phase III trial in a similar population is planned in the USA and Australia. Phase I combination trials of JM-216 with several agents including oral etoposide, paclitaxel, uracil/ftorafur/tegafur, and leucovorin as well as with radiotherapy are ongoing.

DPPE

Compounds with the ability to improve the therapeutic index of currently available cytotoxic agents are under investigation. While DPPE was first synthesized >40 years ago as an antihistamine, it has recently been shown to act as a chemopotentiator enhancing the effects of doxorubicin, daunorubicin, carmustine, cyclophosphamide, and cisplatin while offering cytoprotection to the gut and normal bone marrow progenitor cells [11, 12, 23, 32, 50].

Although its mechanism of action has not been fully elucidated, DPPE is a potent antagonist for novel intracellular (microsomal and nuclear) histamine receptors (H_{IC}) which appear to be involved in the mediation of cellular proliferation [9]. Recent work suggests that DPPE may act as a reversal agent of the P-glycoprotein pump, as well as a mitochondrial poison [61].

An early phase I/II trial of DPPE in combination with various cytotoxic agents yielded evidence of activity in patients who had failed prior treatment with the cytotoxic agent alone [13]. More recently, impressive phase II results for DPPE in combination with doxorubicin have been reported by Brandes et al. in patients with metastatic breast cancer [10]. In 23 evaluable patients a response rate of 70% was observed (95% confidence interval [CI] 47–87%). The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) performed a confirmatory study [45]. In this trial, the overall response rate was 49% (95% CI 31–66%), which included 11% complete and 37% partial responses, which appears to be better than previously reported by the NCIC CTG for single-agent doxorubicin in a similar patient population [68]. It is of note that in the NCIC CTG trial the observed toxicities were similar to those expected for single-agent doxorubicin with the exception of neurological effects attributable to DPPE. These effects included cerebellar signs and hallucinations that were managed with patient sedation during the DPPE infusion.

In view of these encouraging results, the NCIC CTG has initiated a phase III trial comparing the efficacy of doxorubicin plus DPPE to doxorubicin alone in metastatic breast cancer. In addition, phase II results for DPPE in combination with cyclophosphamide in hormone-refractory prostate cancer appear promising, with responses in measurable disease sites and prostate-specific antigen levels, as well as symptom palliation [23]. A randomized phase II trial of cyclophosphamide with and without DPPE in prostate cancer is underway.

Ganglioside vaccines

Progress in the identification of tumor-specific antigens and a better understanding of immune activation processes have led to new optimism for the development of successful cancer vaccines. Carbohydrate antigens abundantly expressed on the surface of most tumors serve as ideal targets for immune recognition and attack [27]. The GM2 and GD2 gangliosides are a class of carbohydrate antigens particularly well suited for cancer immunotherapy [8, 16, 18, 33, 64, 77, 90]. Ganglioside-based vaccines can effectively augment antibody responses against carbohydrate antigens and trigger the killing of antigen-positive tumor cells [53, 55], and there is evidence that vaccine-induced immune responses against a variety of tumor antigens are associated with a more favorable clinical outcome [42, 54]. In a double-blind trial, patients with stage III melanoma who were disease-free after surgery were randomized to receive treatment with the ganglioside GM2/bacille Calmette-Guérin (BCG) vaccine or BCG alone [54]. Vaccination with GM2/BCG was shown to induce primarily immunoglobulin M (IgM) antibodies in most patients. In addition, patients with preexisting or vaccine-induced GM2 antibodies had significantly longer disease-free and overall survival than those without an antibody response. Ganglioside-based vaccines are believed to be best suited for treatment in the adjuvant or minimal residual disease setting where the aim is to eradicate micrometastases and circulating tumor cells [53, 55].

The GM2-KLH/QS21 (GMK) and GM2-KLH/GD2-KLH/QS21 (MGV) vaccines are carbohydrate (ganglioside) vaccines conjugated to an immunogenic carrier protein, keyhole limpet hemocyanin, coadministered with the adjuvant QS-21. In a phase II trial, vaccination with GMK was well tolerated and appeared to induce anti-GM2 IgM antibodies consistently and at sustained levels [39]. The most common adverse events were grade I and II injection site reactions and mild transient fevers. The ECOG Intergroup is currently conducting a phase III trial comparing the relapse-free

and overall survival of patents with resected stage IIB and III melanoma randomized to treatment with either the GMK vaccine or interferon alfa-2b. The selection of the control arm was based on a previous ECOG study that demonstrated that interferon alfa-2b significantly increases relapse-free and overall survival in high-risk resected melanoma patients compared to observation [47]. The EORTC plans to perform a randomized trial of GMK versus observation in stage II melanoma patients.

Clinical studies with the MGV polyvalent ganglioside vaccine are also ongoing. In an initial phase I/II trial in melanoma patients conducted at the Memorial-Sloan Kettering Cancer Center, the MGV vaccine was shown to induce anti-GM2 and anti-GD2 antibody responses (both IgG and IgM) without significant vaccination-related toxicities [17]. Additional clinical trials will focus on tumors known to express both the GM2 and GD2 gangliosides such as small cell lung cancer; other tumor types are under study to determine their level and type of ganglioside expression. Large phase III randomized trials are required to establish the efficacy of the GMK and MGV vaccines because the vaccines are best suited for treatment in the minimal residual disease setting. Demonstration of prolongation of relapse-free and overall survival times are the study endpoints rather than eradication of well-established tumors.

Compounds in early development

Taxanes

The success of paclitaxel therapy in cancer treatment has stimulated interest in further improving its efficacy profile and in identifying new tubulin-active agents. Two taxane analogues (BMS-184476 and BMS-188797) demonstrate greater activity than paclitaxel or docetaxel in a number of rodent solid tumors as well as human xenografts, including one with multidrug resistance expression [81, 82]. In the distal site tumor models L2987 lung carcinoma and HCT/pk colon carcinoma both analogues were superior to paclitaxel by at least a 10-fold cell kill rate. In addition, BMS-184476 was superior to paclitaxel in the human xenograft A2780 ovarian carcinoma and showed modest improvements compared to docetaxel in the clinically derived HOC79 ovarian carcinoma cell line. BMS-188797 demonstrated superiority to paclitaxel in the M109 lung and HOC79 ovarian tumor models, and was moderately better in the A2780 ovarian distal tumor model. Both taxanes are presently in phase I trials evaluating different schedules of administration.

TAS-103

Topoisomerases (Topos) are nuclear enzymes with a critical role during the normal functioning of DNA synthesis and transcription. Currently available agents that target Topo I include topotecan and irinotecan. Topo II inhibitors include etoposide, teniposide, amsacrine, and doxorubicin [29].

Recently, several compounds have been identified which inhibit both Topo I and Topo II [51, 70, 72]. TAS-103 is one such agent with a broad spectrum of antitumor activity and dual Topo inhibition in preclinical models [38, 80, 87]. In a standard assay, TAS-103 was equipotent to camptothecin and SN38 in inhibiting Topo I activity and 40-fold more potent than irinotecan [38, 80, 86]. In addition, in some model systems, TAS-103 was also more potent than etoposide in inhibiting Topo II activity. When compared to the dual Topo inhibitor intoplicine, TAS-103 was more potent in both Topo I and II assays [80].

Preclinical pharmacology studies have shown that TAS-103 has antitumor activity in a variety of animal and human tumor models and is non-cross-resistant with other Topo I or II inhibitors [2, 37, 80, 86, 87]. The in vitro cytotoxicity of TAS-103 was superior to that obtained with irinotecan, etoposide, and intoplicine in the P388 murine leukemia and human epidermoid carcinoma (KB) tumor cell lines. Interestingly, there was lack of cross-resistance in vitro with TAS-103 in cisplatin-, 5-fluorouracil-, and p-glycoprotein-resistant cells [2]. Additionally, there was partial and lack of cross-resistance in P388/CPT cells with decreased Topo I expression and KBNM4 cells with decreased Topo II expression, respectively. In a variety of in vivo studies, TAS-103 exhibited superior or comparable activity to concomitantly tested Topo I or Topo II inhibitors [2, 37, 80, 86, 87]. The models tested included the murine solid tumors B16-melanoma, colon 26, Lewis lung carcinoma, and Yoshida sarcoma model, as well as gastric, colon, breast, NSCLC, and pancreatic human tumor xenografts.

Two ongoing phase I trials with TAS-103 are evaluating different schedules of administration. The maximum tolerated dose of TAS-103 has yet to be defined in either trial and thus far the drug has been well tolerated.

Metalloproteinase inhibitors

Matrix metalloproteinases (MMPs) are a group of zinc-dependent proteolytic enzymes that are overexpressed in many pathological conditions including inflammatory disorders such as rheumatoid arthritis, osteoarthritis, multiple sclerosis, and cancer [4, 52]. In malignant disease, MMPs are capable of degrading the extracellular matrix, the principal barrier for tumor growth and metastasis [14, 88]. Thus MMP inhibitors (MMPIs) offer the potential to intervene in several aspects of tumor progression, including invasion, metastatic spread, and angiogenesis [14, 19, 88].

Malignant progression appears to be related to MMP activation and expression by tumors. Furthermore, the host plays an integral part in tumor growth and spread. There is evidence that host MMPs mediate the remodeling of extracellular matrix accompanying angiogenesis and that tumor cells can activate latent MMPs present in

host stromal tissue, contributing to metastasis [14, 19, 88]. Preclinical studies suggest that MMP-2 and MMP-9 are critical in the process of tumor cell invasion [88], and overexpression of these two MMPs has been shown to correlate with tumor aggressiveness and progression in retrospective studies. In tissue samples from NSCLC patients, a highly significant association was shown to exist between evidence of tumor spread and level of activated MMP-2 [15]. Additionally, elevated MMP-9 expression in surgical specimens from patients with colorectal cancer was linked with metastatic potential and was of prognostic significance for tumor recurrence and treatment outcome [89].

Tissue inhibitors of MMPs (TIMPs) are a class of specific natural protein inhibitors with the crucial role of keeping the damaging potential of the MMPs in check. An imbalance between the expression of activated enzyme and natural inhibitors involving greater MMP levels than TIMP levels has been shown to correlate with the degree of tissue destruction in malignant disease [14, 19, 88]. While the use of TIMPs as therapeutic agents would be impractical given their protein structure, the search for synthetic MMPIs as a rational approach has been ongoing since the early 1980s [19].

BMS-275291 is an orally active MMPI in clinical development. In vitro studies have shown that BMS-275291 has potent activity against key MMPs including MMP-2 and MMP-9 [60]. Importantly, BMS-275291 does not inhibit the release of the tumor necrosis factor receptor nor does it cause joint toxicity in the marmoset monkey. These characteristics may have favorable implications in terms of the compound's expected clinical side effect profile. In particular, BMS-275291 has the potential to cause less joint toxicity than reported for other MMPIs in development [21, 60, 88]. In vivo, oral BMS-275291 reduced the number and size of metastases of the rat HOSP-1 mammary tumor and was active against the murine B-16 melanoma tumor [60]. Furthermore, in vitro antiangiogenic assay results suggest that BMS-275291 may slow tumor growth by inhibiting angiogenesis. A phase I dose-escalation trial with BMS-275291 in healthy volunteers has been completed and studies in patients are planned.

Ras farnesyltransferase inhibitors

New understanding of two fundamental mechanisms of cancer, activation of protooncogenes and inactivation of tumor suppressor genes, has produced insight into the genetics of certain cancers. As a result, new biochemical targets have been identified for therapeutic use in antitumor therapy.

Among the oncogenes, activating mutations of the three functional Ras genes (H-Ras, K-Ras, and N-Ras) appear to occur at high frequency in a number of human cancers. The incidence of mutated Ras has been reported to varying degrees in different tumor types. For example, the incidence of mutated Ras in adenocarcinoma of the pancreas, colon, and lung has been determined to be as high as 90%, 50%, and 30%, respectively [7]. The Ras protein plays a critical role in the transmission of growth signals from the external surface of a tumor cell to internal signaling pathways for regulation of cell proliferation and survival [3, 7, 56]. Mutated Ras proteins are locked in the persistently activated state, thereby contributing to the growth stimulation and malignant properties of cancer cells [3, 7, 44, 56]. The posttranslational modification of Ras, known as farnesylation, enables Ras proteins to anchor to the inner surface of the plasma membrane, which is critical for normal Ras function in signal transduction as well as for its oncogenic activities [44, 48]. Blocking farnesylation results in severe impairment in Ras function and uncoupling of the cell signal transduction cascade due to the inability of the nonfarnesylated protein to anchor to the cell membrane [26, 34, 40, 46, 74]. Thus Ras farnesyltransferase inhibitors (FTIs) should specifically target tumors dependent on oncogenic Ras.

BMS-214662 is a potent and selective FTI currently in clinical trials. When administered by the oral, intravenous, and intraperitoneal routes to tumor-bearing mice, BMS-214662 caused substantial regression of large established tumors [26]. In vivo, intravenous and oral BMS-214662 induced apoptosis in human tumor cells and was curative (cure rate $>50\%$) in a variety of human tumor xenograft models. Tumor regression of $>80\%$ was observed in carcinogen-induced mouse tumors after treatment with BMS-214662. In addition, regression and cure were also seen in the highly resistant HCT-116/VM-26 human colon tumor variant, which is known to be paclitaxel insensitive. The preclinical efficacy data suggest that BMS-214662 has the potential to target human tumors with the H-Ras and K-Ras mutations as well as tumors without Ras mutations.

Conclusions

Intensive research has led to an explosion in the understanding of the molecular basis of carcinogenesis. Consequently, there is renewed interest in identifying new cytotoxic agents with improved or altered efficacy profiles, and there is greater focus on novel target-specific treatment approaches. Preclinical studies suggest that these new compounds have the ability to become effective anticancer therapies, and clinical trials are underway to evaluate the safety and efficacy of these agents. With such innovative and promising developments in cancer chemotherapy there is greater potential now than ever before to advance the treatment of malignant disease significantly.

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