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New cytotoxic agents: a review of the literature

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Abstract

The goal of treatment for patients with advanced cancer is to prolong survival, control symptoms, and reduce disease-related complications. Despite the introduction of many cytotoxic agents during the past decade, only modest improvement in survival has been achieved. In order to urgently improve these situations, new cytotoxic agents as well as molecular-targeted agents are now under investigation. In this article, we reviewed the latest information regarding antitumor activity, toxicity, pharmacokinetics, and clinical application of the new cytotoxic agents.

Keywords: New drug; Cytotoxic; Cancer chemotherapy

1. Introduction

In the mid-1950s, one of the first large-scaled and systematic approaches for anticancer drug screening was organized at the National Cancer Institute (NCI) in the United States [1]. Since then, many anticancer agents have been developed, which has resulted in the gradual and certain improvement of cancer chemotherapy. The recent progress in the identification of new molecular targets in cancer cells has produced new types of anticancer agents, so-called molecular targeting agents, which have been considered to have cytostatic action. However, a number of new cytotoxic agents that have definite activity for various malignancies are constantly under investigation [2–173]. In this article, we summarized the current status of the clinical development of new cytotoxic agents through a computer-based search of the PubMed database and a manual search of abstracts from the past conferences of the American Society of Clinical Oncology. We introduced only agents, which were clinically under investigation.

2. Tubulin-targeted agents

2.1. Taxanes

2.1.1. ABI-007 (abraxane)

ABI-007, an albumin-stabilized nanoparticle formulation of paclitaxel, was designed to overcome insolubility problems encountered with paclitaxel, which eliminates the need for toxic solvents like cremophor [173]. An in vivo study, ABI-007 showed superior efficacy over paclitaxel especially in breast, colon and ovarian cancers [174]. In a phase I trial, ABI-007 was administered once every 3 weeks without premedications. Dose-limiting toxicity consisted of neuropathy, stomatitis, and superficial keratopathy, while no acute hypersensitivity reaction was observed. Pharmacokinetic analyses revealed that maximum concentration (C_{max}) and area under the plasma concentration–time curve (AUC) increased linearly along with the escalation of the ABI-007 dose, and that C_{max} and AUC correlated well with toxicity in the analysis of individual patients [2]. Another phase I trial carried out by weekly administration showed that principal toxicities were neutropenia and neuropathy. Hypersensitivity reaction was also not observed [3]. In this study, ABI-007 exhibited a linear increase of AUC with increasing dose again. In phase II trials, ABI-007 demonstrated a substantial activity against relapsed breast cancer with a response rate of 18–61% [78,79]. Evaluation of ABI-007 for non-small-cell lung cancer (NSCLC), ovarian cancer, and malignant melanoma is currently ongoing. Additionally, a phase III trial comparing the efficacy of ABI-007 with paclitaxel in patients with metastatic breast cancer has completed enrollment [175]. This trial randomized 454 patients to either ABI-007 without premedication or paclitaxel with premedication. Seventy-eight percent of patients had been exposed to prior anthracyclines. Patients treated with ABI-007 achieved a significantly higher objective response rate (33 versus 19%) and longer time to progression (22 versus 16 weeks) than those treated with paclitaxel. In patients treated with ABI-007, grade 4 neutropenia was significantly reduced, and grade 3 or more hypersensitivity reactions were not observed. Although sensory neuropathy was more frequent with ABI-007, it appeared to be manageable. Final results, especially overall survival data, will be presented in the near future.

2.1.2. DJ-927

DJ-927, a novel taxane, has the advantages of high solubility, oral bioavailability and potent antitumor activity. This compound exhibited stronger cytotoxicity than existing taxanes such as paclitaxel and docetaxel against various tumor cells, especially P-glycoprotein (P-gp)-expressing cells [176]. In a phase I trial of DJ-927 administered orally every 3 weeks, myelosuppression was observed as the main toxicity. Preliminary results of pharmacokinetic study indicated dose-proportional absorption over the dose range evaluated. Antitumor effect was obtained in patients with taxane-refractory breast cancer and transitional cell carcinoma of the bladder [4]. These results suggest that DJ-927 might be partially cross-resistant to paclitaxel or docetaxel. Phase II trials of DJ-927 monotherapy are currently ongoing.

2.1.3. CT-2103 (Xyotax)

CT-2103 is a tumor-targeted, polymer–paclitaxel conjugate. This conjugation of paclitaxel to poly-L-glutamate enhanced aqueous solubility. In fact, CT-2103 has 80,000-fold greater water solubility than paclitaxel. In preclinical study, it exhibited excellent antitumor activity in breast and ovarian cancer models [177]. Phase I trials showed that the main toxicities were neutropenia and neuropathy. In pharmacokinetic analysis of CT-2103 administered once every 3 weeks, the