Cancer Treatment Reviews (2008) 34, 81–91

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NEW DRUGS

Novel cytotoxic drugs: Old challenges, new solutions

Gustavo F.V. Ismael [a,b], Daniela Dornelles Rosa [a,c,*], Max S. Mano [a,d], Ahmad Awada [a]

[a] Department of Medical Oncology, Jules Bordet Institute, Université Libre de Bruxelles, Belgium
[b] Department of Haematology and Oncology, Hospital Amaral Carvalho, Jau, Brazil
[c] Paterson Institute for Cancer Research, Wilmslow Road, Manchester M20 4BX, United Kingdom
[d] Department of Medical Oncology, Cliniques Universitaires Saint Luc, Brussels, Belgium

Received 30 March 2007; received in revised form 26 July 2007; accepted 7 August 2007

KEYWORDS
Chemotherapy;
Cytotoxic agents;
Novel drugs;
Drug development

Summary The discovery of cytotoxic agents was revolutionary for anticancer therapy in the last century, improving survival rates and the quality of life of patients with different types of tumours. However, the development of agents that combine efficacy, safety and convenience remains a great challenge, due to the narrow therapeutic index of some drugs, the fact that they may damage not only cancer cells, but also normal and healthy tissue and the occurrence of resistance, limiting anticancer efficacy. Novel cytotoxic agents have brought certain advantages over the conventional ones, such as shorter administration time, mechanisms to overcome drug resistance and lower incidence of adverse events. In this review we highlight the development of promising novel cytotoxic drugs that will hopefully offer not only gains in efficacy, but also in safety, tolerability and convenience in the treatment of patients with cancer.

Introduction

In the last century, the development of cytotoxic agents was revolutionary for cancer therapy. It has made possible to achieve cure for certain neoplasms such as childhood acute leukaemia, Hodgkin's disease, non-Hodgkin's lymphoma, gestational trophlobastic disease and germ cell tumours. Adjuvant treatment with cytotoxic drugs for several types of cancer also offered a clear survival benefit additionally to that obtained with surgical management alone. In patients with recurrent or metastatic disease, cytotoxic agents have demonstrated the ability not only to provide unequivocal tumour control, but also to offer a better quality of life with reasonable symptom relief. However, several limitations became clear, mainly in patients with advanced malignant diseases, where the adverse effects of cytotoxic chemotherapy may preclude its potential benefits.[1]

The development of cytotoxic therapy faces several challenges, as the narrow therapeutic index of some drugs and the fact that cytotoxic drugs damage not only cancer

* Corresponding author. Address: Paterson Institute for Cancer Research, Wilmslow Road, Manchester M20 4BX, United Kingdom. Tel.: +44 79 1372 2813; fax: +44 161 446 3269.
E-mail address: dornellesrosa@hotmail.com (D.D. Rosa).

0305-7372/$ - see front matter
doi:10.1016/j.ctrv.2007.08.001

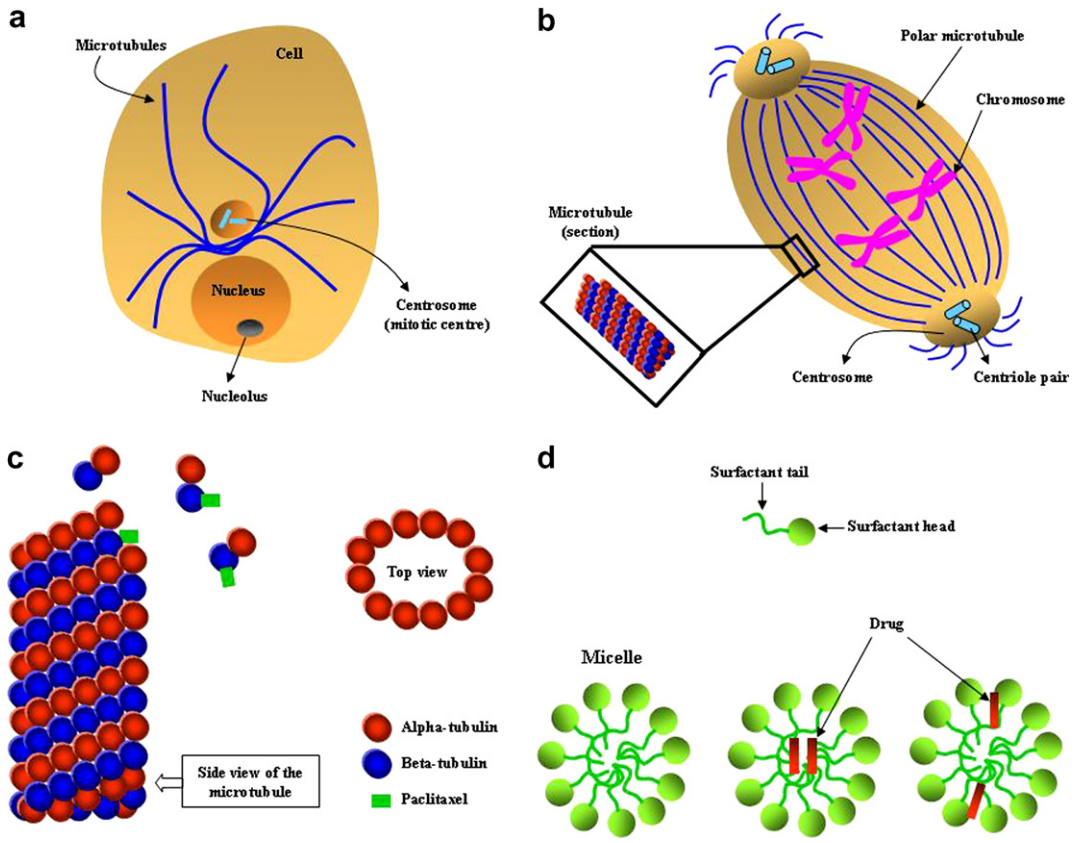

Figure 1 (a) Structure of a cell, with microtubules playing a role in the many cellular functions. (b) During mitosis replicated chromosomes are positioned near the middle of the cytoplasm and then segregated so that each daughter cell receives a copy of the original DNA. To do this cells utilize microtubules (referred to as the spindle apparatus) to pull chromosomes into each cell. The centrioles are paired cellular organelle which functions in the organization of the mitotic spindle during cell division in eukaryotes. (c) Microtubules are composed of heterodimers of alpha- and beta-tubulin. Paclitaxel binds to beta-tubulin on the inner surface of the microtubule, stabilizing it and blocking its normal dynamics. (d) Illustration of a surfactant vehicle. The surfactant heads are hydrophilic moieties and the surfactant tails are hydrophobic moieties. According to the drug hydrophobicity, there may be different loci of solubilization in surfactant micelles.

cells, but also normal and healthy tissue. The occurrence of resistance may also limit its efficacy. The development of agents that combine efficacy, safety and convenience remains a great challenge. A large number of cytotoxic drugs are administered intravenously and some of them may require continuous intravenous infusion, what may be translated into higher costs and the need for hospitalization. Convenience is also an important factor in the choice of treatment for cancer patients; therefore, the development of new and effective oral cytotoxic agents has been a subject of great interest.

The development of novel cytotoxic drugs may improve cancer treatment and patient care. In this review we highlight the development of promising novel cytotoxic drugs that will hopefully offer not only gains in efficacy, but also in safety, tolerability and convenience.

New taxanes

The taxanes are a unique class of hydrophobic antineoplastic agents that exhibit cytotoxic activity by binding to tubulin and promoting inappropriately stable, non-functional, microtubule formation (Fig. 1a–c; Table 1).[2] Over the past two decades, these agents have played a significant role in the treatment of various solid malignancies. However, due to the poor solubility of these compounds, surfactant vehicles have to be included in commercial formulations (Fig. 1d), like the Cremophor EL (CrEL) solvent system, a polyoxyethylated castor oil vehicle that may be responsible for clinically relevant acute hypersensitivity reactions and peripheral neuropathy.[3] A number of strategies to develop formulations of surfactant-free taxanes have been explored, which include albumin nanoparticles, polyglutamates, taxane analogs and prodrugs.

Nab-paclitaxel (nanoparticle albumin-bound paclitaxel)

Nab-paclitaxel (ABI-007; Abraxane™) is a novel formulation of paclitaxel that does not employ the CrEL solvent system. It is prepared by homogenization of paclitaxel in the presence of human serum albumin at a concentration of 3–4%, which results in a nanoparticle colloidal suspension.[4] Enhanced efficacy and reduced toxicity of *nab* paclitaxel when compared with paclitaxel at the maximum tolerated doses (MTDs) were demonstrated in animal models.[5] Several phase