European Journal of Cancer (2013) 49, 245–253

Available at www.sciencedirect.com

SciVerse ScienceDirect

journal homepage: www.ejcancer.info

Review

Microtubule stabilising agents and ionising radiation: Multiple exploitable mechanisms for combined treatment

Carla Rohrer Bley [a,b,*], Polina Furmanova [a], Katrin Orlowski [a], Nicole Grosse [a], Angela Broggini-Tenzer [a], Paul M.J. McSheehy [c], Martin Pruschy [a]

[a] *Department of Radiation Oncology, University Hospital Zurich, Zurich, Switzerland*
[b] *Division of Radiation Oncology, Vetsuisse Faculty, University of Zurich, Zurich, Switzerland*
[c] *Novartis Institutes for BioMedical Research, Novartis Pharma AG, Basel, Switzerland*

Available online 7 June 2012

KEYWORDS
Ionising radiation;
Microtubule stabilising agents
Radiochemotherapy
Epothilones
Taxanes

Abstract Combined radiochemotherapy treatment modalities are in use for many indications and therefore of high interest. Even though a combined modality in clinical use is often driven by pragmatic aspects, mechanistic preclinical-based concepts of interaction are of importance in order to translate and implement an optimal combination and scheduling of two modalities into the clinics. The use of microtubule stabilising agents is a promising strategy for anti-cancer therapy as a part of combined treatment modality with ionising radiation. Traditionally, microtubule targeting agents are classified as cytotoxic chemotherapeutics and are mostly used in a maximally tolerated dose regimen. Apart from direct cytotoxicity and similar to mechanisms of molecular targeting agents, microtubule stabilising agents interfere with multiple cellular processes, which can be exploited as part of combined treatment modalities. Recent preclinical investigations on the combination of ionising radiation and microtubule stabilising agents reveal new mechanistic interactions on the cellular and tumour level and elucidate the supra-additive tumour response observed particularly *in vivo*. The major focus on the mechanism of interaction was primarily based on radiosensitisation due to cell cycle arrest in the most radiosensitive G2/M-phase of the cell cycle. However, other mechanisms of interaction such as reoxygenation and direct as well as indirect endothelial damage have also been identified. In this review we summarise and allocate additive and synergistic effects induced by the combined treatment of clinically relevant microtubule stabilising agents and ionising radiation along a described radiobiological framework encompassing distinct mechanisms relevant for exploiting the combination of drugs and ionising radiation.
© 2012 Elsevier Ltd. All rights reserved.

* *Corresponding author at:* Division of Radiation Oncology, Vetsuisse Faculty, University of Zurich, Winterthurerstrasse 260, CH-8057 Zurich, Switzerland. Tel.: +41 44 635 8487; fax: +41 44 635 8940.
E-mail address: crohrer@vetclinics.uzh.ch (C. Rohrer Bley).

0959-8049/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ejca.2012.05.008

1. Introduction: microtubule stabilising agents

Microtubule targeting agents belong to the most important classes of anti-cancer agents and are subdivided in two groups, according to their mode of action. While microtubule destabilisers prevent the assembly of tubulin heterodimers, microtubule stabilising agents (MSA) prevent the shortening of microtubules resulting in the accumulation of polymerised microtubule bundles and the interference of the mitotic spindle function.[1–4] Experimental evidence concerning the kinetics and mechanism of tubulin-binding as well as the ability to actively promote microtubule function by paclitaxel mimetics has been recently provided using biochemical and Nuclear Magnetic Resonance (NMR) techniques[5] Eventually both classes of microtubule targeting agents alter spindle-microtubule dynamics, which results in a transient or permanent M-phase arrest and the induction of apoptotic cell death or mitotic catastrophe (Fig. 1).[6] In this review we will specifically focus on the mode of interaction between MSA and ionising radiation as part of a combined treatment modality.

Taxanes and epothilones are the clinically most relevant microtubule stabilising agents. The *taxanes* (paclitaxel and docetaxel) have been approved for a broad range of indications, including advanced breast cancer after failure of combination chemotherapy or at early relapse,[7] high grade ovarian cancer in combination with platinum compounds, and primary treatment of non-small cell lung cancer in combination with cisplatin.[8] Furthermore paclitaxel is used in an 'off-label manner' for other tumour types, such as cancer of unknown origin, bladder, oesophagus, gastric, head and neck and cervical cancers (reviewed in Ref. 9). Paclitaxel has also been evaluated clinically for its radiosensitising properties for various tumours[10–14] and drug plasma concentrations in patients. Low concentrations with prolonged exposure during long parts of the course of radiation therapy have been found feasible and tolerated in patients.[12–18] Docetaxel is used as first-line chemo-

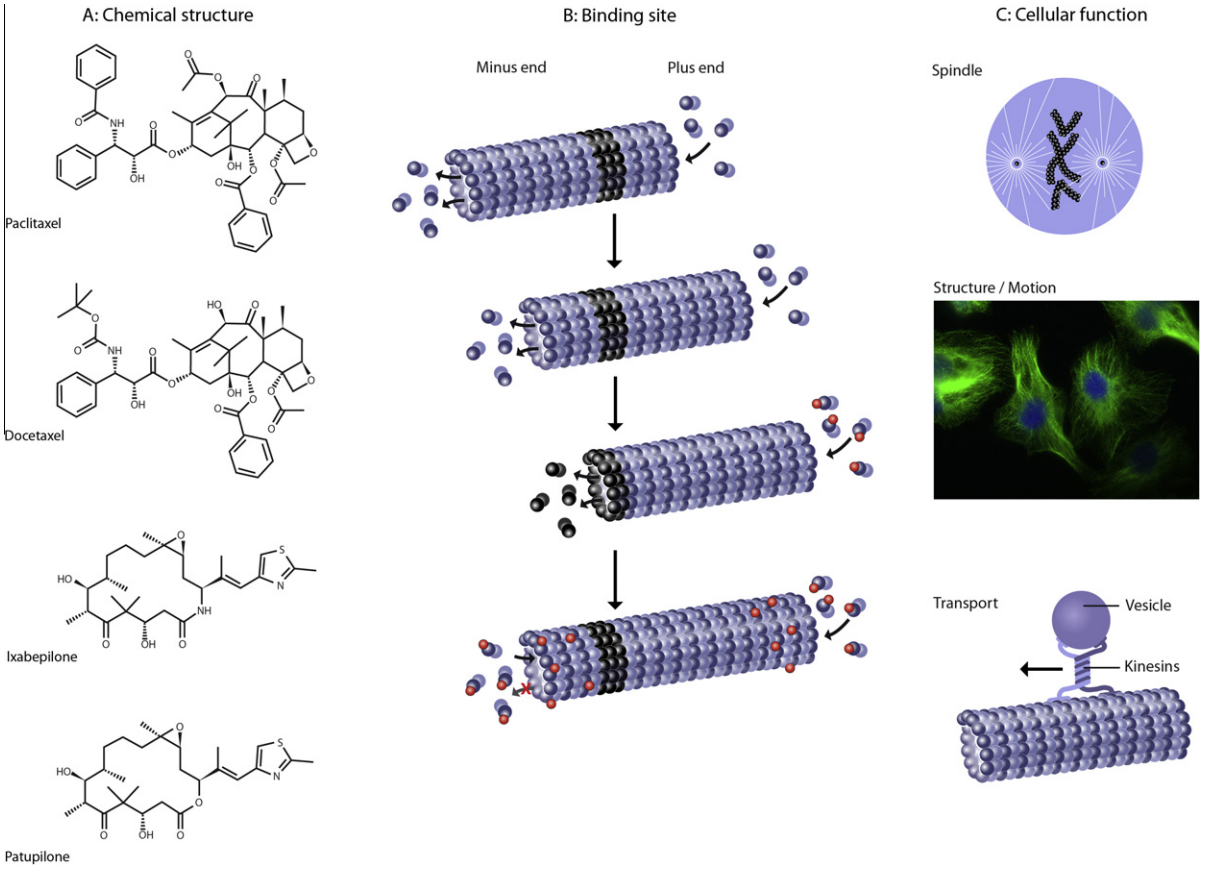

Fig. 1. (A) Chemical structure: The microtubule stabilising agents (MSA) compounds are of complex structure and high chemical diversity. The complex structure of these compounds explains the difficulty for chemical synthesis. (B) Binding site: Microtubules are dynamic structures of α- and β-tubulin molecules arranged in tubular form. The microtubule-stabilising agents of the taxane and epothilone groups bind along the interior surface of the microtubules to the same or an overlapping taxoid-binding site on β-tubulin. Thereby microtubular polymerisation is enhanced and microtubular dynamics reduced. (C) Microtubules interact with various intracellular organelles: In the mitotic spindle, proper alignment and separation of the chromosomes during cellular division is provided by the normal microtubular function. Furthermore cellular structure and motion as well as vesicular transport take place by and along tubular structures.

Download English Version:

https://daneshyari.com/en/article/8445416

Download Persian Version:

https://daneshyari.com/article/8445416

Daneshyari.com