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Pharmacovigilance Working Party (PhVWP)

June 2010 plenary meeting

The CHMP Pharmacovigilance Working Party (PhVWP) held its June 2010 plenary meeting on 21-23 June 2010.

Safety concerns

Discussions on non-centrally authorised medicinal products are summarised below in accordance with the PhVWP publication policy (see http://www.ema.europa.eu/htms/human/phv/reports.htm). The positions agreed by the PhVWP for non-centrally authorised products form recommendations to Member States.

The PhVWP also provides advice to the Committee for Medicinal Products for Human Use (CHMP) on centrally authorised products and products subject to ongoing CHMP procedures at the request of the CHMP. For safety updates concerning these products, readers are referred to the CHMP Monthly Report (see http://www.ema.europa.eu/pressoffice/presshome.htm).

Cisplatin – Risk of increased ototoxicity in patients with genetic variants of TMPT and COMT

Study findings of increased risk of cisplatin-induced ototoxicity in patients with genetic variants of TPMT and COMT need to be further elucidated before recommending changes to use of cisplatin

Recently published study data have suggested an association between genetic variants of thiopurine S-methyltransferase (TPMT) and catechol O-methyltransferase (COMT) and an increased risk of cisplatin-induced ototoxicity (potential to damage the ear). The PhVWP reviewed these data and concluded that further evidence is needed before recommending any changes to the use of cisplatin in medical practice. It was also agreed that no regulatory action is necessary at present, given that the current Product Information already advises on patient monitoring for ototoxicity. The PhVWP will review any data which may become available in the future (see Annex 1 for the Summary Assessment Report).

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Guidelines and general matters

Readers will find below a summary of the principal discussions on guidelines and other general matters of an organisational, regulatory or methodological nature.

CMD(h) & PhVWP Best Practice Guide on Communication and Implementation of Safety Information

The CMD(h) & PhVWP Best Practice Guide on Communication and Implementation of Safety Information was agreed by the PhVWP following its meeting in May and by the CMD(h) at its meeting in June 2010. The revision introduces new procedures underpinning the publication of PhVWP conclusions in the PhVWP Monthly Reports and the implementation of regulatory action by the CMD(h). It also strengthens the involvement of patient and consumer organisations in the review of proposed wordings for Package Leaflets. The Best Practice Guide will be published on the HMA website (http://www.hma.eu/cmdh.html).

Regulatory abbreviations

CHMP – Committee for Medicinal Products for Human Use

CMD(h) – Co-ordination Group for Mutual Recognition and Decentralised Procedures for Human Medicines

EU – European Union

HMA – Heads of Medicines Agencies

PASS – Post-Authorisation Safety Study

PhVWP – CHMP Pharmacovigilance Working Party

PL – Package Leaflet

PSUR – Period Safety Update Report

RMP – Risk Management Plan

SmPC – Summary of Product Characteristics

Annex 1

Summary Assessment Report of the PhVWP June 2010

Cisplatin – Risk of increased ototoxicity in patients with genetic variants of TMPT and COMT

Key message

Study findings of increased risk of cisplatin-induced ototoxicity in patients with genetic variants of TPMT and COMT need to be further elucidated before recommending changes to use of cisplatin.

Safety concern and reason for current safety review

A recent study [1] identified two single nucleotide polymorphisms (SNPs) in the genes encoding thiopurine S-methyltransferase (TPMT) and catechol O-methyltransferase (COMT) in children with cisplatin-induced deafness[1].

The ototoxicity (potential to damage the ear) of cisplatin is well known. According to the current Product Information, cisplatin should not be used in patients with a hearing impairment and audiograms are required before starting treatment with cisplatin and before any new treatment cycle. The ototoxicity of cisplatin is cumulative.

Given the new study findings, the PhVWP reviewed if an increased risk of ototoxicity exists in patients with genetic variants of TMPT and COMT.

Clinical setting

Cisplatin is used in adults and children for the treatment of many cancer types, namely for advanced or metastatic tumours (as monotherapy or in combinations with other cytostatics), such as testicular cancer (as palliative and curative polychemotherapy), ovarian cancer of stages III and IV, bladder cancer, squamous cell carcinoma of head and neck (as palliative treatment), small cell lung cancer and advanced non-small cell lung cancer.

Information on the data assessed

The study by Ross *et al.* [1] consisted of 2 cohorts from Canada. The first cohort of 54 children included 33 cases of serious cisplatin-induced ototoxicity. The second cohort of 112 children included 73 cases of serious cisplatin-induced ototoxicity. The candidate gene studies identified genetic variants in TPMT (TPMT rs12201199: OR = 17.0, 95% CI 2.3–126) and COMT (COMT rs933237: OR=5.5, 95% CI 1.9-15.9) associated with cisplatin-induced hearing loss. While the studied TPMT and COMT genotypes showed relatively high specificity (93%) and positive predictive value (89%), the sensitivity (29%) and the negative predictive value (41%) were rather low.

The study did not identify significant associations with the previously reported associations of cisplatin-induced ototoxicity with polymorphisms in the genes encoding glutathione S-transferases and megalin (low density lipoprotein-related protein 2 (LRP2)).

[1] A SNP is a small genetic variation that can occur within a person's sequence of deoxyribonucleic acid (DNA). TPMT and COMT are enzymes which are involved in the body's metabolism.

It remains unknown at present if there is an association between the genetic variants of TMPT and COMT and the treatment effect of cisplatin in terms of e.g. survival rate.

The PhVWP sought the views of the CHMP Pharmacogenomics Working Party (PgWP) on these study findings. The recently established European Network for Children with Cancer (ENCCA)[2], which is represented in the Agency's Paediatric Oncology Task Force, contributed to the discussion of the PgWP.

Outcome of the assessment

Based on these recently published data, genetic variants of TPMT and COMT are, for the first time, suggested to be associated with an increased risk of cisplatin-induced ototoxicity. The PhVWP reviewed these study data and concluded that further evidence is needed before recommending changes to the use of cisplatin in medical practice. It was also agreed that no regulatory action is necessary at present, given that the current Product Information already advises on patient monitoring for ototoxicity. The PhVWP will review any data which may become available in the future.

References

[1] Ross CJ, Katzov-Eckert H, Dubé MP, Brooks B, Rassekh SR, Barhdadi A, Feroz-Zada Y, Visscher H, Brown AM, Rieder MJ, Rogers PC, Phillips MS, Carleton BC, Hayden MR; CPNDS Consortium. Genetic variants in TPMT and COMT are associated with hearing loss in children receiving cisplatin chemotherapy. Nat Gen. 2009; 41: 1345-1349.

[2] The ENCCA operates under the European Commission's Seventh Framework Programme (FP7) for research initiatives in the EU.