Therapeutic Class Review[SM]

Antineoplastics – Anthracyclines

February 2009

Products for Review:
Anthracyclines (see list of specific agents below)

Dossier Provided by Manufacturer: N/A
Dossier Evaluation: N/A

1 - Dossier missing significant clinical trial(s).
2 - Mfg. provided all relevant trials; Missing pharmacoeconomic model.
3 - Mfg. provided all relevant trials and information.

Executive Summary

- Anthracyclines are a class of cancer medicines that prevent cell division by interrupting cell DNA structure.
- Anthracyclines are used in the treatment of:
  - leukemias: daunorubicin, doxorubicin and idarubicin.
  - breast cancer: epirubicin and doxorubicin
  - ovarian cancer, Kaposi's sarcoma and multiple myeloma: liposomal doxorubicin (Doxil)
  - other solid tumor cancers: doxorubicin
- Anthracyclines are among the most effective chemotherapy treatments available for specific types of cancer.
- Myelosuppression occurs during treatment with anthracyclines regardless of the type of cancer being treated.
- Anthracyclines are known to cause cardiotoxicity, which reduces quality of life and can result in premature death. When cardiotoxicity occurs during therapy, the maximum cumulative dose of anthracyclines needs to be limited, thereby reducing the efficacy of anthracycline chemotherapy.

Evidence

- The scope of this review was limited to comparative studies of anthracyclines.
- A systematic review comparing the efficacy of anthracyclines and subsequent randomized controlled trial comparing doxorubicin with liposomal doxorubicin yielded unreliable evidence. Although the evidence is unreliable, the results are consistent and suggest similar efficacy between products. The evidence was critiqued as unreliable because of open-label trial design and small population size. However, clinically relevant endpoints such as overall survival were evaluated.
- The quality of evidence for the safety endpoints is uncertain, as they were secondary endpoints and it is not clear that the assessors were blinded. The most significant safety endpoints, cardiotoxicity and myelosuppression, were identified *a priori*.

- Five studies evaluated the safety of epirubicin versus doxorubicin in over 1,000 patients but the results were inconsistent with varied patient populations. The results were suggestive of a lower rate of clinical heart failure in patients treated with epirubicin.
- Three studies evaluated the safety of doxorubicin versus liposomal doxorubicin in over 600 patients. A significantly lower rate of heart failure was observed in patients treated with liposomal doxorubicin (Doxil). This effect was consistently demonstrated across different types of cancers.

- It is difficult to determine differences between adverse effects among anthracyclines because adverse effects may be attributed to background chemotherapies.

Consideration in subpopulations

- Doxorubicin (Adriamycin) is the only anthracycline that has been studied in pediatric patients.
- No overall differences in safety or efficacy were observed between patients older than 65 and younger adult patients. [1-5]
- Anthracyclines are Pregnancy Category D. They are excreted into breast milk, so mothers should discontinue nursing prior to receiving these medications. [1-5]
- Dosage should be reduced in patients with impaired hepatic function. [1-5]
- It is recommended that the dosage of daunorubicin and idarubicin be reduced in instances of hepatic or renal impairment. [3,5]

Decision

Liposomal doxorubicin (Doxil) is non-preferred/non-formulary because there are other effective treatments available for ovarian cancer and multiple myeloma that provide a better value for members. (Doxorubicin, epirubicin, and idarubicin are preferred/formulary products).

Products

Drug Products	FDA approval [a]	Patent expiration [b]	FDA approved indications	Usual Dose/Route
Daunorubicin (Cerubidine®) [3]	12/1979	expired	Remission induction in acute nonlymphocytic leukemia (myelogenous, monocytic, erythroid) of adults and for remission induction in acute lymphocytic leukemia of children and adults.	30-45mg/m^2/day IV on days 1-3 per course
doxorubicin (Adriamycin®) [2]	Prior to 1982	expired	Regression in disseminated neoplastic conditions such as acute lymphoblastic leukemia, acute myeloblastic leukemia, Wilms' tumor, neuroblastoma, soft tissue and bone sarcomas, breast carcinoma, ovarian carcinoma, transitional cell bladder carcinoma, thyroid carcinoma, gastric carcinoma, Hodgkin's disease, malignant lymphoma and bronchogenic carcinoma in which the small cell histologic type is the most responsive compared to other cell types	60-75 mg/m^2 IV q 21 days monotherapy 40-60 mg/m^2 IV q 21-28 days in combination therapy
Doxorubicin liposome (Doxil®) [1]	11/1995	expired	• Ovarian cancer • AIDS-related Kaposi's Sarcoma • Multiple Myeloma	• Ovarian cancer: 50 mg/m^2 IV every 4 weeks • AIDS-related Kaposi's Sarcoma: 20 mg/m^2 IV every 3 weeks • Multiple Myeloma: 30 mg/m^2 IV on day 4 , every 3 weeks
Epirubicin (Ellence®)[4]	9/1999	expired	Axillary node tumor involvement following resection of primary breast cancer	100 to 120 mg/m^2 IV q 3-4 weeks
Idarubicin (Idamycin®)[5]	9/1990	expired	Idarubicin HCl injection in combination with other approved antileukemic drugs is indicated for the treatment of acute myeloid leukemia (AML) in adults.	12 mg/m^2 IV daily for 3 days

[a] Date applies to approval date for the original brand name medication where there are now generics available.
[b] Based on patents listed in the Orange Book as of 12/09/2008.

References

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6. Porter CA, Rifkin RM. Clinical benefits and economic analysis of pegylated liposomal doxorubicin/vincristine/dexamethasone versus doxorubicin/vincristine/dexamethasone in patients with newly diagnosed multiple myeloma. *Clin Lymphoma Myeloma*. 2007 Apr;7 Suppl 4:S150-5.
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8. van Dalen EC, Michiels EMC, Caron HN, Kremer LCM. Different anthracycline derivates for reducing cardiotoxicity in cancer patients. *Cochrane Database of Systematic Reviews* 2006, Issue 4. Art. No.: CD005006. DOI: 10.1002/14651858.CD005006.pub2.

9. Stebbing J, Delaney G, and Thompson A. Breast cancer (non-metastatic). *BMJ Clin Evid* 2007;11:102.

10. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Ovarian Cancer v.1.2008. Available at: http://www.nccn.org. Accessed on 1/7/09.

11. National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Multiple Myeloma. v.2.2009. Available at: http://www.nccn.org. Accessed on 1/7/09.

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