FRESH FROM THE PIPELINE

Oxaliplatin

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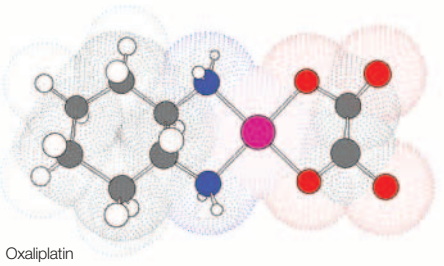

Oxaliplatin

Oxaliplatin (Eloxatin; Sanofi-Synthelabo) is the first platinum-based anticancer drug to be approved for the treatment of colorectal cancer, a major cause of cancer deaths worldwide. Following European approval in 1999, has approval of oxaliplatin by the US FDA in August 2002 set it on the road to becoming a blockbuster?

Each year, about one million patients worldwide are diagnosed with colorectal cancer, which has been estimated to be the fourth largest cause of cancer deaths[1]. For several decades, chemotherapy of the disease has been based on traditional cytotoxic drugs, in particular intravenous 5-fluorouracil (5-FU), a drug whose metabolites disrupt RNA synthesis, and also inhibit thymidylate synthase, thereby impairing DNA synthesis[2]. However, response rates to 5-FU regimens as a first-line treatment for colorectal cancer are modest[2]. More recently, 5-FU in combination with leucovorin (LV), which prolongs the inhibition of thymidylate synthase by 5-FU, and irinotecan (Camptosar; Pfizer), which inhibits cell division by targeting DNA topoisomerase I, has shown significantly improved response rates[2]. Nevertheless, there is still a pressing need for further agents active in colorectal cancer, in particular for those patients who fail to respond to current treatment regimens or who develop drug resistance.

Basis of discovery

The anticancer activity of cisplatin (FIG. 1) — the first platinum-based drug to enter clinical use — was discovered fortuitously in the late 1960s. The detailed mechanism by which platinum-based drugs kill cancer cells is still under investigation, but broadly speaking these agents form adducts with cellular DNA, which disrupt essential processes such as DNA replication and transcription (FIG. 1), leading to apoptosis[3–5].

Although cisplatin has a wide spectrum of anticancer activity, it does have significant side toxicity, and its clinical use can also be limited by the existence or development of resistance. Several thousand platinum-based compounds have been synthesized in an attempt to overcome these problems. Substitution of the two ammine moieties of cisplatin with the diaminocyclohexane (DACH) group led to compounds that had good antitumour activity and lack of cross-resistance with cisplatin, but which were poorly water-soluble, limiting their potential for clinical development[4]. Further modifications aimed at improving water solubility by replacing the chloride moieties of cisplatin resulted in the discovery of oxaliplatin[4] (FIG. 1).

Drug properties

Oxaliplatin has a broad spectrum of anticancer activity and a better safety profile than cisplatin[4,5]. It also shows a lack of cross-resistance with cisplatin or carboplatin (another widely used platinum-based compound), which is thought to result from the chemical and steric characteristics of the DACH–platinum–DNA adducts[4,5]. Observations such as the demonstration that, in contrast to cisplatin and carboplatin, oxaliplatin was active against several colon cancer cell lines in the National Cancer Institute's Anticancer Drug Screen Panel[6] provided impetus for its clinical evaluation in this indication. Moreover, preclinical studies showed that oxaliplatin in combination with 5-FU has greater *in vitro* and *in vivo* antiproliferative activity than either compound alone in several tumour models, including colon cancer[7].

Trial data

In a randomized, three-arm, controlled study, oxaliplatin (85 mg per m^2; 2-hour infusion) in combination with an infusional schedule of 5-FU/LV was compared with the same dose and schedule of 5-FU/LV alone, and with oxaliplatin alone, in patients with advanced colorectal cancer who had relapsed/progressed during or within six months of the current standard first-line therapy of bolus 5-FU/LV and irinotecan[7]. In a planned interim analysis of 459 patients enrolled in the study, those treated with the combination of oxaliplatin and infusional 5-FU/LV had an increased response rate (9%) compared with patients given infusional 5-FU/LV alone (0%) and oxaliplatin alone (1%)[7]. In addition, an estimated two-month increase in median time to progression was observed in patients receiving oxaliplatin and infusional 5-FU/LV compared with infusional 5-FU/LV alone[7].

More recently, oxaliplatin (85 mg per m^2; 2-hour infusion) in combination with an infusional schedule of 5-FU/LV has demonstrated superior activity over irinotecan and bolus 5-FU/LV as a first-line therapy for metastatic colorectal cancer[8].

Indications

In the United States, oxaliplatin, used in combination with infusional 5-FU/LV, is indicated for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has recurred or progressed during or within six months of completion of first-line therapy with the combination of bolus 5-FU/LV and irinotecan[7]. In Europe, oxaliplatin in combination with 5-FU/LV is indicated as a first-line treatment for patients with metastatic colorectal cancer. ▶

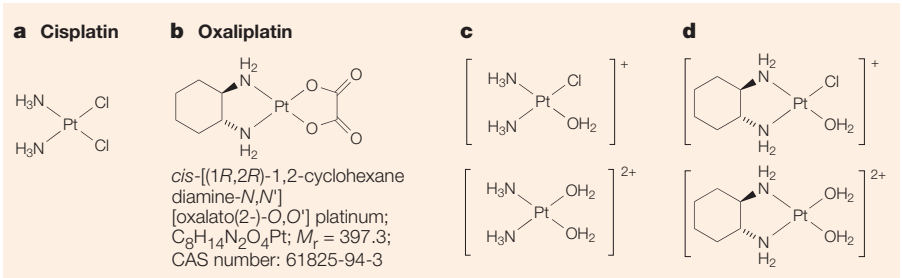

Figure 1 | **Platinum-based anticancer drugs. a** | Cisplatin. **b** | Oxaliplatin. **c** | In physiological solutions, cisplatin is non-enzymatically converted (by displacement of the chloride moieties) to active derivatives, including those shown. Active complexes form adducts with genomic DNA, in particular by attacking the N7 position of guanine bases[3–5]. The first attack generates mono-adducts, which can react with another DNA base, resulting in the formation of both intrastrand (in particular) and interstrand Pt–DNA crosslinks that inhibit DNA replication and transcription[3–5]. **d** | Oxaliplatin is also converted (by displacement of the oxalate ligand) to give active complexes, such as those shown, that react with DNA bases, resulting in the formation of intra- and interstrand Pt–DNA crosslinks[4,5,7]. Differences between the steric and chemical properties of DNA lesions formed by cisplatin and those formed by oxaliplatin are thought to underlie the differences in the activity of cisplatin compared with oxaliplatin; for example, the lesions due to oxaliplatin might be more effective at inhibiting DNA synthesis.

OXALIPLATIN | MARKET ANALYSIS

For decades, the market for drugs for colorectal cancer (CRC) was dominated by 5-FU and its biomodulator LV, but as both of these agents have been available as generic drugs for a considerable time, the value of the CRC market remained small in relation to the size of the patient population. However, since 1995, irinotecan has been launched in most major markets, initially as a second-line treatment for patients who had failed 5-FU treatment for their metastatic CRC, and subsequently as a first-line treatment in combination with 5-FU. The arrival of an active new agent increased the value of the CRC market, with CRC drugs achieving sales of >US $1.4 billion in the seven major markets in 2002, a figure that is forecast to rise considerably in the next decade, reaching >US $5 billion by 2012 (FIG. 2), in part owing to increasing sales of oxaliplatin.

Oxaliplatin was initially launched in France in 1996 and subsequently in the rest of Europe in 1999 and, more recently, in the United States in August 2002. It is the first platinum-based drug to demonstrate convincing clinical activity against CRC. Oxaliplatin is in direct competition with irinotecan, and sales of the latter have faltered during the past year as oxaliplatin has penetrated the market. Although clinicians view both agents as having similar activity in CRC, the toxicity profile favours oxaliplatin. In addition, the complexities of optimal 5-FU administration have potentially aided the adoption of oxaliplatin by clinicians. In contrast to irinotecan, for which clinical development was driven by US clinicians who have favoured bolus 5-FU administration, the majority of clinical studies evaluating oxaliplatin, and those used for regulatory submissions, have been with 5-FU infusion, which is now considered to be a more active administration schedule than bolus 5-FU.

Sales for oxaliplatin in 2002 were US $ 389 million, and the impact of the US market — in which oxaliplatin provides clinicians with a much-needed novel and effective treatment option — is clearly reflected by the considerable increase in sales in 2003, which had already reached US $607 million for the first three quarters.

Other new agents for CRC

Capecitabine (Xeloda; Roche), an orally administered fluoropyrimidine, is now registered for use in CRC and is beginning to replace intravenous 5-FU/LV. With time, we forecast that capecitabine will take a large proportion of the 5-FU patient share and cause a further increase in the size of the CRC market. Oxaliplatin-plus-capecitabine treatment is now under investigation, and is likely to become popular with clinicians and patients, owing to the improved ease of administration and a superior side-effect profile.

Although cytotoxic drugs will continue to be the mainstay of chemotherapy for CRC, novel targeted agents are about to enter the market. Two have recently been submitted for approval for metastatic CRC: bevacizumab (Avastin; Genentech/Roche), an antibody targeted at the vascular endothelial growth factor, and cetuximab (Erbitux; ImClone/Merck), an antibody targeted at the epidermal growth factor receptor, which was approved in Switzerland in November 2003. Neither of these agents have demonstrated activity as single agents; indeed, it is difficult to justify single-agent evaluation in a patient population for which several active treatment options exist. This means that such novel agents will not replace existing cytotoxic therapies but will add on to treatment regimens with a consequent increase in the total value of the CRC market (FIG. 2), particularly as these agents are expensive biologicals. Clinical evaluation of oxaliplatin in combination with these targeted agents is underway.

Future market for oxaliplatin

Colorectal cancer. Approval as a first-line treatment in the United States will further expand the oxaliplatin market. In addition, final data from the MOSAIC study[9] released earlier this year demonstrated a significant benefit of the addition of oxaliplatin to 5-FU/LV adjuvant treatment (following potentially curative surgery for early stage (non-metastatic) disease) in reducing the risk of recurrence of CRC. These data will form the basis of approval for adjuvant use of oxaliplatin, which will drive further growth of the drug into this large patient population. If and when widespread approval is granted in these more lucrative first-line and adjuvant markets, we forecast that oxaliplatin will reach blockbuster status, with sales of >US $1.6 billion by 2012.

Other cancer indications. As with CRC, oxaliplatin might forge a niche as a therapy for cancers that are not responsive to other platinum-based drugs. Phase III studies of oxaliplatin are also ongoing in pancreatic cancer and gastric cancer as are earlier-phase studies in non-small-cell lung cancer and breast cancer. Clearly, success in such large markets could markedly increase the value of oxaliplatin.

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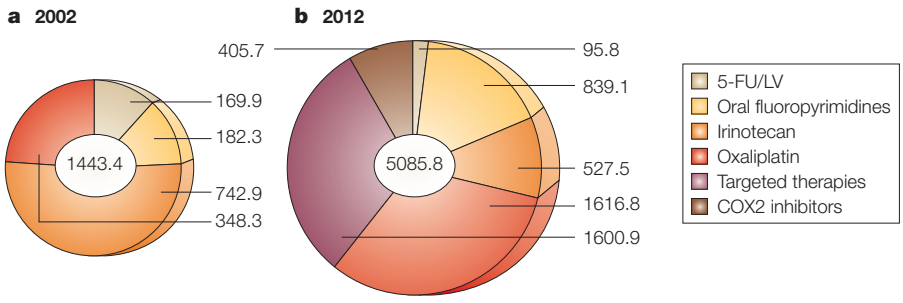

Figure 2 | **Market for drugs to treat colorectal cancer in US $ million.** Data are for the seven major pharmaceutical markets (United States, France, Germany, Italy, Spain, United Kingdom and Japan). Targeted therapies include antibodies targeted against vascular endothelial growth factor and against the epidermal growth factor receptor. COX2, cyclooxygenase 2; 5-FU, 5-fluorouracil; LV, leucovorin.