Distribution of Anticancer Drugs in River Waters and Sediments of the Yodo River Basin, Japan

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Featured Application: This work gives an overview of the present status of anticancer drugs in the environmental water of the Yodo River basin, a specific populated area in Japan. The results indicate importance of application of high-tech treatment(s) including advanced oxidation processes at sewage treatment plant for efficient removal of the discharged drugs.

Abstract: This article reviews the pollution status of anticancer drugs present in the Yodo River basin located in the Kansai district of Japan, covering both the soluble and insoluble (adsorbed on the river sediments and suspended solids) levels. Procedures ranging from sampling in the field and instrumental analytical methods to the data processing for mass balance estimation of the target basin are also described. All anticancer drugs concerned with this article were detected in sewage and river waters, where the presence of bicalutamide (BLT) was identified at considerably high concentrations (maximum 254 ng/L in the main stream, 151 ng/L in tributaries, and 1032 ng/L in sewage treatment plant (STP) effluents). In addition, sorption distribution coefficient ($\log K_{d}$) values showed a tendency to become higher in the silty sediments at Suita Bridge than in the sandy sediments at Hirakata Bridge; these trends were supported by the results of the laboratory-scale sorption experiment. STPs were concluded to be the main sources of the anticancer drug load in the river, and a mass flux evaluation revealed that the effect of attenuation in the river environment was small. The effectiveness of ozonation in the sewage treatment process for removal of these anticancer drugs was further confirmed. The present article should be of value for facilitating the environmental risk assessment of a wide range of drugs in a broader geographical area.

Keywords: anticancer drugs; urban river basin in Japan; river water; river sediment; sorption distribution coefficient ($\log K_{d}$); sewage treatment plants (STPs); ozonation

1. Introduction

The emerging problem of the pollution of river environments by pharmaceuticals and personal care products (PPCPs) has received a large amount of attention [1–3]. Pharmaceuticals are designed to have specific physiological effects on target areas of the body. Concern is therefore rising about their toxic effects on ecosystems when discharged into environmental water, even when they are present at low concentrations. Furthermore, their impacts on human health via residues contaminating drinking water should be taken into consideration [4–7]. Generally, the concentrations of these compounds are low (roughly in the range from ng/L to µg/L) worldwide [7–9]. Even in this low concentration range, however, there have been reports of the endocrine-disrupting chemicals that have serious environmental impacts, such as the feminization of male fishes [10,11].

PPCPs include different groups of compounds typified by their chemical characteristics, structure, mechanism of action, mode of action, and their therapeutic use to treat specific diseases. Particularly,
anticancer drugs are emerging as an area of growing interest because of their promotion of a long lifespan via the suppression of human death through their use as a chemotherapy \[12,13\].

Human life is changing in response to recent developments in science and technology. In Japan, cancer has been the country’s top cause of death since 1981, accounting for 29% of all deaths in 2015. This was nearly double the rate of the second-highest cause of death, heart disease (15%) \[14\]. In addition, because of the aging of the Japanese population \[14\], the number of cancer patients who need treatment is likely to increase in future. Increasing numbers of new pharmaceuticals for chemotherapy \[15\], which, along with surgery and radiotherapy, is an important treatment for cancer, have been developed in recent years \[16\]. The use of anticancer agents in clinical situations is also increasing, whereas the rates of adoption of surgical therapy and chemotherapy in Japan have stayed about the same \[17\].

According to their mechanisms of action, anticancer drugs are mainly classified into alkylating agents, antimetabolites, hormone antagonists, cytotoxic antibiotics, antimitotics, cytotoxic quinolones, and topoisomerase inhibitors. Because all of these anticancer drugs have physiological activity and are highly cytostatic, there are many concerns about their cytostatic effects on aquatic ecosystems and on organisms living in the aquatic environments \[12,18–20\]. In fact, an anticancer drug, tamoxifen (TAM), inhibited the reproduction and growth of *Daphnia* at 120 ng/L \[21\] and showed a predicted no-effect concentration of 81 ng/L for fish, plankton, and algae \[22\]. In addition, anticancer drugs are present in the sediments in river environments. Therefore, serious pollution problems sometimes arise from contaminated river water because of the exposure of benthonic organisms and bioaccumulation in predators such as fish along the ecological chain through predation \[23,24\]. The sedimented substances affect not only river environments, but also marine environments, and humans are at risk when they eat fish polluted with them through bioaccumulation \[25–27\].

At present, the pollution aspect of anticancer drugs in Japan has been analyzed only in the very limited area surrounding the Yodo River since 2009 \[13,28–31\]. Their occurrence in the river water and sediments, including from hospital and sewage treatment effluents \[13,28,32\], their fate after discharge \[31\], and their attenuation properties \[29,30\], were reported in a separate fashion. The time has come to make an overview of the status of anticancer drugs in the environmental water of the Yodo River basin.

The aim of this article is to summarize the state of anticancer drugs in the regional river water and sediments in the subcatchment of the Yodo River basin in Japan, providing an invaluable fundamental basis for further spreading of the related studies into a wide range of PPCPs across a wide area to achieve the final goal for conducting effective environmental risk assessments of discharged PPCPs in the future.

## 2. Materials and Methods

### 2.1. Sampling of Environmental Waters and Sediments

The question of primary importance is of how to select the sampling field to determine the distribution of pharmaceuticals in the environmental waters. For this purpose, considering the spreading out of the geographical region to core cities throughout Japan, the sampling areas in the Kansai district of Japan were selected; the locations were on the right bank of the middle-to-downstream region of the Yodo River \[32\] and on two other rivers, the Kanzaki and the Ai, and their tributaries. This area, known as the Kanzaki–Ai River basin, covers an important commercial and urban area of about 790 km\(^2\) in Osaka and Hyogo prefectures and is home to 2 million people \[33,34\].

To collect three different types of waters (river, tributary, and sewage treatment plant (STP)), 13 sampling sites consisting of six river sites (R1 to R6), four tributary sites (T1 to T4), and three STP sites (S1 to S3) (Figure 1) were set in the Kanzaki–Ai River basin. The sampling site at the Suita Bridge (R5) was set as the farthest downstream boundary. One sample was basically taken per site, but two
effluents, S3(1) and S3(2), were sampled at S3, compiling 14 samples per each sampling time. Names of the sampling sites were used for identification (ID) of the samples. A conventional activated sludge (CAS) process followed by chlorination for disinfection was used in all STPs except S3 where ozonation (8.6 mg/L ozone) was used after partial CAS. The properties of the STPs including treatment process are shown in Table 1 [35]. Annual flow rates and BOD (biological oxygen demand, mg/L) at the sampling sites in the Kanzaki–Ai River basin are listed in Table 2 [30,36]. Stainless-steel pails were used to collect water samples, while a stainless-steel bottom sampler was used for river sediment samples collected at R5 (Suita Bridge) and R6 (Hirakata Bridge). All samples were transferred in separate glass bottles, transported to the laboratory within 2 h and kept at 4 °C under dark. Analysis of the concentration of the target anticancer drugs in each sample was started within 24 h after collection by filtration through a GF/B glass fiber filter (pore size, 1-μm) for separation of liquid from the suspended solids [37].

The surveying anticancer drugs was conducted once in the four seasons in 2013 and 2014; on 4 April (spring), 29 July (summer), 18 December (late autumn), and 4 February (winter). Sampling days were selected on rain-less days accompanied by 2 more ahead fine days (rainfall ≤ 1 mm) [38].

**Figure 1.** Locations of sampling sites in the Kanzaki–Ai River basin (reproduced from [30]). (Information of the sampling sites of S1–S3 are shown in Table 1, while those of a combined group of R1–R6 and T1–T4 are shown in Table 2.)

**Table 1.** Information of sewage treatment plants (STPs) located in the Kanzaki–Ai River basin (Figure 1) (reproduced from the data in [30]).

| Sample-ID | Service Area (ha) | Service Population (Person) | Flow Rate (m³/day) | Treatment Process |
|-----------|-------------------|-----------------------------|--------------------|-------------------|
|           |                   |                             | Mean               | SD                |
| S1        | 5459              | 494,974                     | 256,110            | 31,285            |
| S2        | 453               | 50,732                      | 17,050             | 2355              |
| S3(1)     | 3550              | 415,364                     | 128,497            | 11,876            |
| S3(2)     |                   |                             |                    |                   |

CAS: Conventional activated sludge; AO: Anaerobic/aerobic; A2O: Anaerobic/anoxic/aerobic.
2.2. Selection of Anticancer Drugs and Their Quantification

With consideration of their highly frequent therapeutic use in Japan and high excretion rates in unchanged form [39,40], this article focused on the following six anticancer drugs listed in Table 3. Bicalutamide (BLT) is an active antiandrogen medication used to treat prostate cancer. Capecitabine (CAP) is a chemotherapy medication used to treat breast cancer, gastric cancer, and colorectal cancer. Cyclophosphamide (CP) is a chemotherapy medication used to treat ovarian cancer, breast cancer, and small cell lung cancer. Doxifluridine (DFUR) is a chemotherapy medication used to treat gastric cancer, intestinal cancer, and breast cancer. TAM is a medication used to treat breast cancer. Tegafur (TGF) is a chemotherapeutic prodrug of 5-fluorouracil and is used to treat various types of cancer. Once these anticancer drugs are discharged in the environment, their distribution will be affected by their individual physicochemical properties; of these, surface charge due to differences in $pK_a$, pH, and hydrophobic properties estimable from logP were of importance to establish their solubility and degree of adsorption onto organic matters and sedimented materials. The properties of the target anticancer drugs are summarized in Table 3.

Table 3. Details of the target anticancer drugs typified by their action mechanisms (reconstructed based on the data listed in [41]).

| Compound             | CAS Registry Number | Molecular Formula | Molecular Mass (g/mol) | Structure | $pK_a$ | logP  | Action Mechanism                  |
|----------------------|---------------------|-------------------|------------------------|-----------|--------|-------|----------------------------------|
| Bicalutamide (BLT)   | 90357-06-5          | C$_{18}$H$_{24}$F$_4$N$_2$O$_2$S | 430.4                  | ![Structure Image](structure.png) | 11.5    | 4.1   | Antiandrogens                    |
| Tamoxifen (TAM)      | 10540-29-1          | C$_{26}$H$_{20}$NO | 371.5                  | ![Structure Image](structure.png) | 8.7     | 5.1   | Antiestrogens                    |
| Cyclophosphamide (CP)| 50-18-0             | C$_{5}$H$_{10}$Cl$_{2}$N$_2$O$_2$P | 261.1                  | ![Structure Image](structure.png) | 2.8     | 0.2   | Nitrogen mustard analogues      |
| Capecitabine (CAP)   | 154361-50-9         | C$_{15}$H$_{22}$FN$_3$O$_6$ | 359.4                  | ![Structure Image](structure.png) | 5.4     | 1.0   | Pyrimidine analogues             |
| Doxifluridine (DFUR) | 3094-09-5           | C$_{8}$H$_{11}$FN$_2$O$_5$ | 246.2                  | ![Structure Image](structure.png) | 7.6     | −0.7  | Pyrimidine analogues             |
| Tegafur (TGF)        | 17902-23-7          | C$_{8}$H$_{9}$FN$_2$O$_3$ | 200.2                  | ![Structure Image](structure.png) | 7.6     | −0.6  | Pyrimidine analogues             |

CAS: chemical abstracts service; $pK_a$: logarithmic acid dissociation constant; logP: octanol-water partition coefficients.
For quantitative analysis of CP and TAM, gas chromatography (GC) combined with mass spectrometry (MS) was used initially after purification and derivatization [42–44]. Recent in-depth quantification of these drugs together with the other anticancer drugs was achieved by the simultaneous combination of procedures known as solid-phase extraction (SPE) and liquid chromatography–mass spectrometry (LC-MS/MS) [16,45–47], with special care taken for differences in the protocols applied for the liquid and the solid samples. The concentration and purification steps of the anticancer drugs in the liquid samples were performed by SPE [13,31]. In the case of the river sediments and the suspended solids (solid state samples), solvent extraction of the adsorbed materials was achieved by sonication and filtration [31,48,49] prior to analysis.

The final step of measurement was to separate and quantify the target pharmaceuticals by the LC-MS/MS system equipped with an appropriate PC for regulation and calculation. The optimized MS/MS parameters are summarized in Table 4. The cone voltages for detection of the hormone antagonists (BLT and TAM) were somewhat higher than the other anticancer drugs, while lower cone voltages were adequate for the analysis of the antimetabolites (CAP, DFUR, and TGF), which have similar pyrimidine-analogous structures.

Table 4. LC-MS/MS parameters for the target anticancer drugs (reproduced from [30]).

| Compound          | Retention Time (min) | Precursor Ion (m/z) | Product Ions (m/z) | Cone Voltage (V) | Collision Energy (eV) | Ionization Mode |
|-------------------|----------------------|---------------------|--------------------|------------------|-----------------------|-----------------|
| Bicalutamide (BLT) | 14.8                 | 429.3               | 255.2              | 30               | 16                    | −               |
| Tamoxifen (TAM)   | 17.9                 | 372.4               | 72.3               | 45               | 15                    | +               |
| Cyclophosphamide (CP) | 10.2               | 261.2               | 106.2, 139.9, 181.9, 233.4 | 35 | 15 | + |
| Capecitabine (CAP) | 12.4                 | 360.4               | 174.2, 244.2       | 25               | 16                    | +               |
| Doxifluridine (DFUR) | 2.0                | 247.2               | 73.0, 99.1, 117.0  | 15               | 12                    | +               |
| Tegafur (TGF)     | 2.8                  | 201.2               | 71.0, 131.1        | 15               | 18                    | +               |

Product ions in italics were used for quantification.

Quantification of the anticancer drugs was done by subtracting the blank data from the data given by the spiked sample solutions for accounting matrix effects and loss during sample extraction [30,50]. Similarly, recovery rates were calculated from the deviations between the spiked data and the standard data to perform calibration. Recovery rates varied in the range of 63–124% for river water, 52–116% for STP effluent, 23–112% for river sediment, and 33–122% for suspended solids. These values were mostly similar to the values previously reported for pharmaceuticals in river and sewage samples [48,51]. The values of limit of detection (LOD) and limit of quantification (LOQ), which are important for estimating the sensitivity of the methods, were calculated based on the concentrations at signal-to-noise ratios of 3 and 10 [52,53]. The estimated LOD and LOQ values for liquid samples were in ranges of 0.1–0.4 and 0.3–1.4 ng/L, respectively, but the corresponding values for solid samples appeared in larger ranges of 2.4–13 and 8.2–42 ng/kg, respectively.

2.3. Estimation of Sorption Distribution Coefficient (LogKd) and Mass Balance

The sorption distribution coefficients (logKd) between the liquid samples and the solid samples were determined as log(Cs/Cw) in accordance with the previous reports [54,55], where Cs (ng/kg) is the concentration of pharmaceuticals in the solid samples and Cw (ng/L) is the concentration of pharmaceuticals in the liquid samples.

Experimental sorption of the target anticancer drugs onto the river sediments was done separately by following the procedure as described previously [56–58] as well as OECD guideline No. 106 [59]. Sediment samples were suspended in ammonium acetate buffer (pH 7) containing a known amount of the anticancer drugs (0–200 µg/L), and the mixtures were shaken reciprocally for 24 h at 20 °C in the
dark to prevent photolysis [56,57]. After incubation, each solution was recovered by filtration through a GD/X glass fiber filter and the concentrations of the anticancer drugs were measured by LC-MS/MS. In the cases for the experimental sorption, the log\( K_d \) values for the river sediment were determined from the slope of the linear regression lines produced by the initial and equilibrated concentrations in the dissolved phase and the dry weight of the adsorbent [24,60,61].

For estimation of the mass balance of the target anticancer drugs discharged into the Kanzaki–Ai River basin, the mass flux (g/day) of each anticancer drug at each site was calculated by multiplying the detected concentration by the mean river flow rate or the mean STP discharge rate in terms of m\(^3\)/day. The flow rates at the sampling sites are listed in Tables 1 and 2. Total mass flux for each drug was calculated by numerical summation of the mass flux values from the upstream region to the farthest downstream boundary site at the Suita Bridge (R5). The mass balance of each drug was then estimated as a percentage of the mass flux for that drug at this boundary site.

3. Results and Discussion

3.1. Distribution of Anticancer Drugs in River Waters and STP Effluents

Table 5 summarized the detected concentrations of the target anticancer drugs. All anticancer drugs were present in both the river waters and the STP effluents [30]. The median concentrations of BLT, TAM, CP, CAP, DFUR, and TGF were 32 ng/L, N.D., 2 ng/L, 2 ng/L, N.D., and N.D., respectively, in the main stream samples, 30 ng/L, N.D., 3 ng/L, 1 ng/L, N.D., and N.D., respectively, in the tributaries, and 245 ng/L, N.D., 10 ng/L, 6 ng/L, N.D., and 23 ng/L, respectively, in the STP effluents (excluding the ozonation STP). The concentrations of BLT, CP, CAP, and TGF in the STP effluents were thus several times higher than those in the river waters. In the previous studies, CP and TAM were detected in the range of N.D. to several tens of ng/L in river water [12,45,62,63] and from N.D. to 100 ng/L in the STP effluent [12,19,47,63–65]. On the other hand, in the case of BLT, which is frequently used to treat prostate cancer [66], the maximum concentrations were about 2–10-fold higher than the concentrations of the other drugs: 254 ng/L in main stream samples, 151 ng/L in tributaries, and 1032 ng/L in STP effluents (excluding ozonation). Detection frequencies in the main stream and tributary samples were quite high (83–100%) for BLT and CAP, but low—in the range of 6–44%—for DFUR, TAM, and TGF. The corresponding values for CP were moderate (56–63%). In the cases of TAM and DFUR, their detected concentrations appreciably decreased in the STP effluents. This indicates easiness of degradation of these anticancer drugs by the usual treatment at STPs. Although concentration differences were detected among the seasons, the orders were about the same throughout the year. In addition, the quantities of water to be treated at these STPs and the river flow rates in the target basin were fairly stable throughout the year [36]. Consequently, the data shown in this article suggest that the target six anticancer drugs were being used all year round.

The concentrations of the anticancer drugs detected in the STP effluents (BLT, CP, CAP, and TGF) tended to be several times higher than those in the river waters. Clarification of the levels and mass balances of all discharged anticancer drugs in the urban river environment, together with the optimization of clean-up treatments at STPs, will be helpful in maintaining the health of residents in the sampling area. In the effluent samples from the STP that used ozonation, the mean concentrations of all anticancer drugs ranged as low as from N.D. to several ng/L, which were roughly one-tenth to one-hundredth of the concentrations detected in the effluents from STPs with chlorination after biological treatment (Table 5). This kind of observation was in accord with those of the previous studies [67–69], indicating the effectiveness of ozonation treatment for removing a wide range of pharmaceutical compounds, including anticancer drugs from water samples.
Table 5. Detection of the target anticancer drugs in river waters and STP effluents (n = 24 (main stream), n = 16 (tributary), n = 10 (STP effluent), n = 10 (STP effluent—ozonation)) (reproduced from [30]).

| Compound     | Sample Type                  | Concentration (ng/L) | Frequency (%) |
|--------------|------------------------------|----------------------|---------------|
|              |                              | Mean (SD) Median     | Max | Min |
| Bicalutamide (BLT) | Main stream                 | 55 (71) 32 254       | N.D. 83 |
|              | Tributary                    | 46 (43) 30 151       | N.D. 94 |
|              | STP effluent                 | 316 (303) 245 1032   | 49 100 |
|              | STP effluent (ozonation)     | 13 (20) 5 41         | N.D. 50 |
| Tamoxifen (TAM) | Main stream                 | 5 (16) N.D. 76       | N.D. 33 |
|              | Tributary                    | 8 (12) N.D. 33       | N.D. 44 |
|              | STP effluent                 | 1 (3) N.D. 9         | N.D. 10 |
|              | STP effluent (ozonation)     | N.D. (0) N.D. N.D.   | N.D. 0 |
| Cyclophosphamide (CP) | Main stream               | 3 (5) 2 16          | N.D. 63 |
|              | Tributary                    | 4 (6) 3 20          | N.D. 56 |
|              | STP effluent                 | 11 (7) 10 20        | N.D. 90 |
|              | STP effluent (ozonation)     | 7 (10) 3 22         | N.D. 50 |
| Capecitabine (CAP) | STP effluent               | 3 (4) 2 20          | N.D. 88 |
|              | Tributary                    | 3 (4) 1 16          | N.D. 100 |
|              | STP effluent                 | 6 (3) 6 11          | 2 100 |
|              | STP effluent (ozonation)     | 2 (2) 4 N.D.        | N.D. 50 |
| Doxifluridine (DFUR) | Main stream             | 2 (8) N.D. 39       | N.D. 8 |
|              | Tributary                    | 1 (3) N.D. 12       | 6 |
|              | STP effluent                 | 1 (3) N.D. 8         | N.D. 20 |
|              | STP effluent (ozonation)     | N.D. (0) N.D. N.D.  | N.D. 0 |
| Tegafur (TGF) | Main stream                 | 5 (13) N.D. 56      | N.D. 25 |
|              | Tributary                    | 6 (12) N.D. 35      | N.D. 25 |
|              | STP effluent                 | 20 (16) 23 49       | N.D. 70 |
|              | STP effluent (ozonation)     | 4 (8) N.D. 17       | N.D. 25 |

N.D.: Not detected.

3.2. Allocation of Anticancer Drugs in the Sediment and Suspended Solid Samples

The occurrences of anticancer drugs in the solid state samples (river sediments and suspended solids) at Suita Bridge (R5) and Hirakata Bridge (R6) are summarized in Figure 2 [31]. Three anticancer drugs (BLT, TAM, and CAP) were detected at appreciably higher concentrations in the suspended solids at 628, 13–658, and 231 µg/kg, respectively, with higher levels at the Hirakata Bridge than at the Suita Bridge. In the river sediments, however, only lower levels of the same two anticancer drugs (BLT and TAM) and DFUR were detected at 391, 42–250, and 392 ng/kg, respectively, with no clear difference between both of the sites. These profiles indicate an abundance of particles which have high affinity to the anticancer drugs in the river water. However, the concentration of the suspended solids at the Hirakata Bridge (2.6 mg) was about 30% of that of the Suita Bridge (9.0 mg). Based on these results, the pollution load of the anticancer drugs originating from the suspended solids was concluded to be not very large. Localization of DFUR and CAP in the different solid samples is attributable to the difference in the affinity of these drugs to the particles present in the samples.

The sorption property of the present anticancer drugs on the river sediments was further characterized by a sorption experiment [31]. The measured log$_{K_d}$ values varied in a range from −0.4 to 2.1 (Table 6). The actual log$_{K_d}$ values of the individual anticancer drugs in the sediments at the Hirakata Bridge and the Suita Bridge were 0.4 and 1.4 (BLT), 2.1 and 1.6 (TAM), 0.8 and 0.6 (CP), −0.4 and 0.1 (CAP), 0.9 and 1.5 (DFUR), and 1.3 and 0.4 (TGF), respectively. The concentrations of the anticancer drugs at the Suita Bridge showed a tendency to become higher than those at the Hirakata Bridge. This result is attributable to differences in the particle types in the sediment: sandy sediment at the Hirakata Bridge (moisture content of 9% with 79% sand, 3% silt, and 0% clay) and silty sediment at the Suita Bridge (moisture content of 49%, but no available data for its composition). Similar observation has also been reported in previous studies dealt with different pharmaceuticals [60,67].
These observations suggest that the anticancer drugs present in the river water environment were mainly distributed in the liquid phase. The major reason of this biased view could be ascribed to the difference in their octanol–water partition coefficients, log\(K_{\text{OW}}\) (log\(P\)) values [68], which ranged from −0.7 to 5.1 (Table 1). However, the overall results suggest that not only the log\(P\) values but also the electric charge and its density (associated with the functional groups in the anticancer drugs) participate as factors which determine the degree of adsorption onto the particles [37,69].

When the log\(K_d\) values were estimated for the anticancer drugs in the solid state samples, positive values were detected only in the case of BLT; 4.3 for the suspended solids at the Hirakata Bridge, while 0.8 for the river sediments at the Suita Bridge. The value at the Suita Bridge was similar to that obtained by the laboratory experiment for the river sediments at this bridge, suggesting the possibility that the capacity for sorption onto the river sediments could be predicted by estimation. However, the log\(K_d\) values for the other anticancer drugs whose concentrations were below LOD remained undetermined. This lack of log\(K_d\) values or abundance of concentrations below LOD was the consequence of attenuation due to photodegradation by sunlight and biodegradation through water flow over time [28,70]. The higher positive value for the suspended solids compared to the sediments was in association with the relatively low abundance of the suspended solids.

### 3.3. Source Distribution of Anticancer Drugs

Based on the data compiled in this article, the major load source distribution of anticancer drugs in the Kanzaki–Ai River basin could be estimated. The amount of the individual anticancer drugs flowing from the upstream region (S3, R6) to the farthest downstream sampling site (R5) was determined.
The contribution of each load source to the total mass flux was then calculated as mass flux (%) (Figure 3) [30].

Figure 3. Source distribution of anticancer drugs in the Kanzaki–Ai River basin (abbreviation of each anticancer drug is shown in Table 1) (reproduced from [30]).

For all anticancer drugs except TAM, the contribution of STP effluents as pollutant loading sources was large, amounting about 50–92% of the total load, while the contribution of tributaries was as low as in the level of 0.3–2.0%. A typical example of these mass flow transitions by using the case of BLT as a representative anticancer drug is shown in Figure 4 [30]. Consequently, STP effluent was strengthened to be a major contributor to the pollution of river waters by the target anticancer compounds in the surveyed area.

Figure 4. Transition of mass flows (g/day) from upstream to downstream regions in the Kanzaki–Ai River basin for bicalutamide (BLT). N.A.: not available (reproduced from [30]).

These results also showed that the contribution of STP effluents to the total load of TAM was low (19%; Figure 3). In the case of this anticancer drug, the contributions of the main stream and tributaries were higher than the other anticancer drugs. Recently, a screening assessment of TAM has been published [71], along with a review of its ecotoxicological effects [21,22,72]. However, because of a lack of enough information about the fate of this drug after its discharge into environmental waters, more extended investigations are needed to explain the findings mentioned above. In addition, the bulk of the contributions remained as unassigned in the total mass flux of the target anticancer drugs came
from the upstream points surveyed in the main stream [73]. In the present article, pollution loads might have come from areas beyond the sample collection points, because the Kanzaki River originates from a branch on the right bank of the Yodo River [74]. For this reason, advanced water-processing techniques should be introduced not only at STPs located in the middle and downstream reaches, as well as the upstream reaches, to decrease entire pollution loads and improve the water quality of the Kanzaki–Ai River system.

3.4. Mass Balance of Anticancer Drugs

The mass balance for each target anticancer drug in the Kanzaki–Ai River basin could further be estimated by calculation of percent contribution of total efflux load in the influent load through the farthest downstream boundary site (R5). In the present article, the total efflux load for each anticancer drug was obtained by summation of the mass fluxes from two data sets from Kanzaki River (R3 and T4) and Ai River (R1, S1, T1, T2, and S2). The influx load was estimated as the load passing through the boundary site (R5). The resulting mass balance data are shown in Figure 5 [30].

![Figure 5](image-url)

**Figure 5.** Mass balances of anticancer drugs in the Kanzaki–Ai River basin. N.A.: not available. The abbreviation of each anticancer drug is shown in Table 1 (reproduced from [30]).

The load of CP was reduced by 70% as it was flowed downstream indicating occurrence of attenuation, but the attenuation rates for the other anticancer drugs were smaller, roughly in the range of 15–50%. BLT has a high recalcitrant property and detected at high concentrations in the river waters [75,76]. Therefore, some of the anticancer drugs are attenuated while being flowed to the lower reaches, but the rate of the attenuation is slow and such anticancer drugs become the matter of environmental pollution.

Today, STPs play an important role for maintaining the quality of river water environment. In Japan, the contributions of pharmaceutical components, including endocrine-disrupting chemicals (EDCs) such as estrogen, to the pollutant loads in the river waters range from 50% to nearly 100% [73,77], because of the high coverage of sewerage systems by STPs (more than 90% of urban areas) [35]. As a result, STPs become indispensable facilities responsible for reducing the levels of pharmaceuticals included in sewage effluent [16]. The conventional activated sludge (CAS) process, which is often used as the convenient physicochemical and biological treatment at STPs, covers 35% of biological water treatment in Japan [35]. However, its insufficient ability to eliminate anticancer drugs at STPs, as described above, necessitates the introduction of additional post-treatment technologies. Importance of such an advanced water treatment systems at STPs is becoming widely recognized [78–80], because of high power for removing not only PPCPs but also other chemicals such as EDCs [81], persistent organic pollutants (POPs) [82], bacterial pathogens, and viruses [83].
3.5. Advanced Technologies for Removal of Anticancer Drugs

Advanced oxidation treatment [84], membrane treatment [85], and hybrid treatment of adsorption with ozonation and/or UV [86] are representative treatments, which can be effectively used to solve the water pollution problems and ensure the safety of the water environment. Examples of these treatments applied to CP, one of the target anticancer drugs discussed in this article, are listed in Table 7.

| Category | Technology | Treatment | Source | Initial Concentration (pH) | Temperature (°C) | % Removal | Reference |
|----------|------------|-----------|--------|---------------------------|-----------------|-----------|-----------|
| Membrane separation | MBR | Supplemented wastewater COD 1750 mg/L | 5 µg/L (pH 7–8) | 25–32 °C | 60% (153 days) | Seira et al., 2016 [87] |
| | NF | MBR-effluent | 1.513 µg/L | 20 °C | 92% | Wang et al., 2009 [88] |
| | RO | MBR-permeate | 0.185 µg/L | 27–28 °C | 41% | Kovalova et al., 2013 [89] |
| Adsorption | PAC | Effluent | 2 µg/L | 27–28 °C | 28% | Kovalova et al., 2013 [86] |
| | AC | Surface water | 2 µg/L | 12 °C | <95% | de Ridder et al., 2009 [89] |
| Chemical Oxidation | O₃ | Hospital wastewater | 0.64 (g/g DOC) | 20°C | 33% | Kovalova et al., 2013 [86] |
| | O₃ (3g/L) | Artificial wastewater (36 mg O₃/g DOC) | 10 µg/L | 20°C | 100% (pH11) | Li et al., 2016 [92] |
| | O₃ (10 mg/L) | Wastewater effluent (10.0 mg/L DOC) | 5 µg/L (pH 7.2) | - | ca. 70% | Ferre-Aracil et al., 2016 [93] |
| | O₃ (43.9 g/m³) (55.3 g/m³) | Hospital wastewater | (pH 8.1–8.2) | 20°C | 97% | Ferre-Aracil et al., 2016 [93] |

NF: nanofiltration; RO: reverse osmosis; MBR: membrane bioreactor; PAC: powdered activated carbon; AC: activated carbon, DOC: dissolved organic carbon.
Ozonation is one of the techniques known as advanced oxidation processes (AOPs), which use \( \text{HO}^\cdot \) generated from ozone (O\(_3\)). \( \text{HO}^\cdot \) is the second strongest oxidant, after fluorine. Combined techniques with UV (O\(_3\)/UV), \( \text{H}_2\text{O}_2 \) (O\(_3\)/\( \text{H}_2\text{O}_2 \)), and both (O\(_3\)/UV/\( \text{H}_2\text{O}_2 \)) were also developed and applied to remove CP. UV and \( \text{H}_2\text{O}_2 \) are known to increase the rate of \( \text{HO}^\cdot \) formation [89]. Application of these treatments to remove the anticancer drugs has an outstanding benefit of higher degradability with lower toxicity of the reaction byproducts, but is accompanied by the shortcomings of the undesirable consumption of the oxidizing agents by the associated scavengers in the samples and the possible formation of less biodegradable byproducts and/or conversion into still more highly toxic byproducts. Additional treatments are sometimes still needed to achieve complete mineralization. These processes are thought to be cost-effective and their practical utilization has already started at some model STPs, as described in this article.

Removal of the target compounds by adsorption is the simplest, most cost-effective, and versatile way. Various kinds of materials are usable as adsorbents, such as activated carbon, mesoporous silica, zeolite, biochar, carbon nanotubes, clays, graphene oxide, chitosan, biomass wastes, and functionalized resin [90]. In addition, two types of operation systems, batch-wise and continuous, are also available practically. By using the affinity of the special adsorbent for a specific drug, selective removal of recalcitrant drugs could be achieved.

This article is concentrated to a specific area in Japan where the population is high. Evidently, there are similar areas in many other countries with a high population and a rather limited flow of streams, where concentrations of anticancer drugs may thus be more or less similar to those presented in this article. Finally, the present article should have value for conducting future ecotoxicity assessments of anticancer drugs and the risks they pose to human health via drinking water.

4. Conclusions

The present article contributed summative clarification of the distribution of six anticancer drugs (BLT, TAM, CP, CAP, DFUR, and TGF) in the river waters and sediments of the Yodo River basin in Japan, including effluents from sewage treatment plants (STPs). In the year-round survey, all anticancer drugs were detected at medium concentrations in the range of N.D.–32 ng/L in the river water and N.D.–245 ng/L in the STP effluents, with the highest levels for BLT (254 ng/L in river water and 1032 ng/L in the STP effluents). STPs were the primary sources of anticancer drugs in the river water, and the attenuation effect of the river environment was small. Ozonation was effective in removing these drugs. BLT, DFUR, and TAM were also detected in the river sediments at maximum concentrations of 391, 392, and 250 ng/kg, respectively. In addition, the sorption distribution coefficient \( (\log K_d) \) in river sediments appeared to be higher in the silty sediments at Suita Bridge than in the sandy sediments at Hirakata Bridge, in accord with the results of the laboratory-scale sorption experiment. The present article provides fundamental data as an initiative for conducting risk assessments of environmental pharmaceuticals in a wider geographic area.

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