

Anticancer drugs are the first cause of drug-induced liver injury in a reference hospital

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Author contribution statement: AP, SL, ML, ZM, RA, ML, and XF participated in the concept and design of the study, review and analysis of data, and writing and editing of the manuscript. The rest of the authors participated in the review and analysis of data and in the editing of the manuscript.

Word count: 2997 words

Number of figures and tables: 2 tables

Abbreviations: DILI (drug-induced liver injury), ALT (aspartate aminotransferase), ALP (alkaline phosphatase), TBL (Total Bilirubin), ULN (upper limit of normal), RUCAM (Roussel Uclaf Causality Assessment Method) DI-ALH (Drug-induced autoimmune-like hepatitis)

Data availability statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Financial support: no financial support for this study.

Conflicts of interest: RA acted as advisor for Bayer, Boeringher-Ingelheim, InnoCare, Janssen, Obseva, Novo-Nordisk, Roche, Silence-Therapeutics, Sanofi, Vivet Therapeutics and has a research Grant from Gedeon Richter/Preglem S.A, Willmar Schwabe GmbH & Co. ZM has received speaker fees from Orphalan, Abbvie and Gilead and consultant fees from Orphalan, Alexion and Deep Genomics. SL acted as advisor and speaker for Abbvie and Gilead and recieved grants from Gilead. MCL received advisory fees from Intercept/AdvanzPharma, GSK, Ipsen and speaker fees from Intercept/AdvanzPharma, Cymabay. XF acted as advisor for Gilead.

Ethics Approval statement: The study was submitted and Approved by the Ethics Committee of our Institution. Except for AP and XF, study investigators could only access patient codes and were not able to retrieve patients' personal data. Signed informed consent was required.

Key words: antineoplastic drugs, oncologists, diagnosis

Abstract

Drug-induced liver injury (DILI) is a challenging liver disorder for hepatologists. We aimed to assess the pattern and causes of DILI in a tertiary hospital. We registered prospectively all patients referred with suspicion of DILI from 2018 to 2023. A total of 106 patients fulfilled the diagnostic criteria (30 caused by paracetamol were excluded; total number 76). The pattern of liver injury was **hepatocellular in 55 (72%)**. Drugs causing DILI were antineoplastic (26%), antibiotics (24%), analgesics (13%), and recreational drugs (10%). Regarding clinical outcomes, 39 (51%) required hospitalization and 7 (9%) underwent a liver transplantation or died from acute liver injury. We identified 126 additional patients with DILI due to immune check-point inhibitors who were not referred to a liver disease specialist. Antineoplastic drugs have become the first cause of DILI in hospitals. A multidisciplinary approach and specific educational tools to increase DILI awareness are needed among **different** specialists.

Abstract word count: 150

Introduction

Idiosyncratic drug-induced liver injury (DILI) is a diagnostic challenge for liver disease specialists and its relevance is increasing due to the wide use of new approved drugs in the last decades (1). The incidence of DILI ranges between 5 and 20 cases per 100.000 person years, which may be considered low, but the true incidence is most likely underreported (1,2). The latter may be explained by the fact that most published studies are retrospective and a significant proportion of patients are not referred to liver disease specialists.

From a clinical point of view, DILI can present in diverse patterns (hepatocellular, cholestatic or mixed). Diagnosis is difficult since other causes of liver test abnormalities need to be excluded and, moreover, a significant proportion of patients are taking a number of drugs that makes very difficult to establish causality. One important issue regarding DILI is its outcome. When clinically significant DILI occurs, around 10% of patients may develop liver failure and in some areas of the world, DILI is the first indication for urgent liver transplantation (3).

Regarding the type of drugs implicated in DILI, antibiotics have been the main cause of idiosyncratic DILI in most studies to date (4). Nevertheless, in the last decade, an increasingly incidence of DILI caused by anticancer drugs is being reported (1). Thus, our main aim was to assess the causes and pattern of DILI in a referral center during the last 5 years, as well as to determine which variables are related to clinical outcomes.

Patients and methods

Patients

We prospectively registered all patients with a suspicion of DILI referred to our Liver Unit from January 2018 to June 2023. If a diagnosis of DILI could be established, the patients were included in the observational cohort study.

Diagnosis of DILI was established in patients fulfilling one of the 3 following criteria (5): 1) ALT >5 times ULN or 2) Alkaline Phosphatase (ALP) > 2 times ULN or 3) ALT > 3 times ULN and TBL > 2 times ULN. Other potential causes of liver test abnormalities (alcohol, viral hepatitis -including hepatitis E-, autoimmune hepatitis, biliary obstruction, liver steatosis) were

excluded. The causality RUCAM score was calculated for each patient; only cases scored ≥ 3 were considered.

All cases were assessed for drug-induced autoimmune-like hepatitis (DI-ALH) using the criteria published by García-Cortés et al (6,7), and classified as DI-ALH **if the following criteria were present: autoantibodies, elevated IgG and a liver biopsy suggesting autoimmune hepatitis (lymphoplasmacytic portal infiltrate and interfase hepatitis).**

The following variables were recorded: epidemiological (age, sex, BMI, ethnicity), potential causes of liver disease (**alcohol intake > 20 g/d for women and > 30 g/d for men-**, metabolic dysfunction-associated steatotic liver disease), liver tests (AST, ALT, ALP, GGT, TBL), drugs and doses that patients were taking in the last 12 months (as well as date of initiation/interruption), intake of herbal and dietary supplements and clinical outcome (need for hospitalization, transplantation or dead, resolution).

In addition, we retrieved all patients who received immune check-point inhibitors (ICIs) **in our center** during the same period of time (January 2018 to June 2023) from the Pharmacy Department and investigated those who presented ALT elevation (≥ 5 times ULN) during therapy.

Statistical analysis

Categorical variables are expressed as n (%) and quantitative variables as median and interquartile range (IQR). Groups were compared using the Mann-Whitney U test for continuous variables when appropriate and the Fisher exact test for categorical variables. For multivariate analysis we used the forward stepwise selection method (including variables with statistical significance at univariate analysis). Statistical significance was established as a 2-sided P value of 0.05. Statistical analyses were performed using either SPSS version 20.0 (IBM, Chicago, IL, USA).

Ethics

The study was approved by our Ethical Committee (ref HCB/2018/1115 and HCB/2010/6144). All patients were informed of the protocol and signed an informed consent before inclusion in the study.

Results

A total of 159 patients were referred to our Liver Unit with suspicion of DILI between January 2018 and June 2023. Of these 106 fulfilled the diagnostic criteria of DILI. Since in 30 patients the cause of DILI was paracetamol (intrinsic DILI), the final cohort consisted of 76 patients.

The main characteristics of patients are shown in Table 1. Median age was 58 years (IQR 42–65) and 32 (42%) were female. In 68 patients (90%) the pattern of DILI was hepatocellular; **49 (65%) patients had ALT > 10 ULN**. Median liver test results at the presentation of DILI were: ALT 1723 U/L (IQR 392–2994 U/L); ALP, 176 U/L (IQR, 126–232 U/L); bilirubin 16,9 mg/dL (IQR, 12–20 mg/dL); and INR, 1,41 (IQR 1,16–1,76). Antinuclear antibodies were present in 20 (28%) and anti-smooth muscle in 24 (32%) of patients. Jaundice and symptoms highly suggestive of liver injury (nausea, abdominal pain) were common, whereas rash or fever were only present in a small proportion of patients (Table 1). RUCAM score was 3–5 (possible) in five cases, 6–8 (probable) in 49 and > 8 (highly probable) in 22.

It is important to notice that 55 (72%) patients were on more than one prescription drug at time of DILI diagnosis: 9 (12%) with 2 drugs, 9 (12 %) with 3, 17(22%) with 4, and 20 (26%) with ≥ 5. We considered DILI was caused by a single medication in 69 (91%) cases and by multiple agents in 8 (10,5%) (Table 2).

The most common class of medicines involved were anticancer drugs (20, 26%), followed by antibiotics (18, 24%). DILI was caused by analgesics in 9 cases (12%) and by recreational drugs in 7 (9%). Regarding individual drugs, those more commonly implicated were amoxicillin-clavulanate in 9 (12%) cases, nivolumab in 5 (7%), isoniazid in 5 (7%) and atorvastatin in 4 (5%).

A liver biopsy was available for 38 (50%) of the 76 patients; 2 (8%) of them fulfilled criteria for DI-ALH (Table 2). Both patients (and an additional one fulfilling 2 criteria for DI-ALH caused by infliximab) were treated with prednisone, with a favorable response.

Clinical outcomes

The severity of the liver injury assessed by the DILI severity index (8) was mild in 31 patients (41%), moderate in 23 (30%); in the remaining patients 22 (29%) it was severe or fatal (Table 1).

A total of 39 patients (51%) were hospitalized because of symptoms (jaundice, severe nausea or vomiting) and/or INR > 1,5. Variables associated with hospital admission were age, AST and ALT levels, bilirubin, leucocytes and skin rash (Table 1). The only variable that was independently associated with hospital admission was bilirubin (b 0.21, 95% CI 1.08-1.4, p =0.001).

After a median follow-up of 13 months the final outcome was resolution in 69 patients (90%). Contrarily, 7 patients (10%) underwent liver transplantation or died (1) due to liver failure. In univariate analysis bilirubin, and leucocyte counts were associated with liver failure (data not shown).

ICIs causing DILI not referred to our Liver Unit

ICIs are considered as a cause of indirect drug-induced liver injury. Surprised by to the low number of patients with DILI caused by these drugs in our registry, we decided to retrieve all cases of aminotransferase increase (ALT x 5 ULN) during ICIs therapy in our center within the same period of time (2018-2023). We detected 138 patients: 19 cases related to atezolizumab, 35 to bevacizumab, 22 to ipilimumab, 37 to nivolumab and 25 to pembrolizumab. Of these, 126 (91%) fulfilled the diagnostic criteria of DILI. Thus, if these patients had been referred to our unit, anticancer therapies would represent more than 90% of DILI cases.

Discussion

More than a decade ago, the main cause of DILI in patients referred to hepatologists were antibiotics and analgesics (4). In the last decade, there has been a constant increase in the

development of new antineoplastic agents, with approval of new agents every year. Importantly, the hepatotoxicity of these agents has not always been well defined and in most instances side effects are described after approval.

In our series, the most common anticancer drugs causing DILI were ICIs inhibitors and protein kinase inhibitors. We also found that most cases of DILI caused by ICIs were directly managed by oncologists and were never seen by liver disease specialists, reinforcing the idea that anticancer therapy is by far the main cause of DILI in a hospital setting. Moreover, it is possible that mild liver tests abnormalities caused by other anticancer agents (protein-kinase inhibitors, aromatase inhibitors) are only managed by oncologists. The implications of these findings are relevant, since decisions on the management of cancer patients in the setting of DILI are not always straightforward and may directly impact disease outcomes. This is not only applicable to ICIs but other anticancer treatments. Overall, it is important to reinforce DILI detection and management systems, with an active collaboration among hepatologists, oncologists (and other clinical areas), as well as hospital pharmacovigilance programs. This collaboration would ultimately lead to an improved capacity for case detection and causality evaluation, contributing to safety signal generation (9,10).

In other medical areas, there are already specialists devoted to the assessment and management of cancer drug toxicity. Thus, there is an International CardioOncology Society (11) and similarly, most nephrology units have staff members specialized in the assessment and treatment of the different side effects caused by anticancer drugs (such as tubular interstitial nephritis or glomerulonephritis) (12). **Among hepatologists, it would be also relevant to increase the number of specialists with a high expertise in DILI, due to the growth of liver toxicity caused by anticancer drugs.**

We found that drug-induced autoimmune-like hepatitis (DI-ALH) occurred in around 5% of patients who had a liver biopsy, a similar figure than that recently reported (2,3%) by the Spanish and LatinAmerican DILI Registries (6). This figure was significantly higher if only 2 of the suggested criteria for DI-ALH (biopsy and autoantibodies) were applied. However, given the relatively high prevalence of autoantibodies in the general population and in particular in patients with DILI, it seems reasonable to apply more stringent criteria.

Another finding of our study is the prevalence of recreational drugs as cause of DILI. We identified 7 (10%) of these patients and more importantly, the majority were classified as

severe (and one died). **The slightly higher prevalence of recreational drugs in our cohort compared to others may be explained by the fact the Hospital is a toxicology referral center and also by the high consumption of cocaine in the Barcelona area (13).**

Regarding clinical outcomes, our data are in accordance with most studies (1-4). It is well known that the severity of DILI is higher due to referral bias in patients admitted to tertiary centers as compared with population-based studies. **In our study this figure could be even higher due to the fact that our center is a referral for acute liver failure.** Nevertheless, it should be kept in mind that severe hepatitis may occur and liver failure reaches around 10% in this particular population. Our sample size did not allow to establish which variables were independently related to death or liver transplantation, but bilirubin was clearly associated to as hospital admission, particularly when the pattern of DILI is hepatocellular.

Our study has some strengths. First, it is an observational prospective study in which all patients were followed by the same physicians (XF, AP). Second, diagnosis of DILI was made based on the RUCAM score and validated by two different liver disease specialists (MCL, SL, JSP). The study has also several limitations. First, the sample is not representative of all cases of DILI occurring in the hospital: only a minority of DILI caused by anticancer drugs were referred to our Unit and it is most likely that other mild cases were not seen by our team. Moreover, in patients who were not referred to our Unit, we only search for ALT elevations in those who were treated with ICIs; this may introduce a bias since other not reported causes of DILI were not included. In addition, although hepatocellular DILI is the most common phenotype produced by ICIs, cholestatic or mixed type are occasionally also seen and these other cases might have been missed using the ALT criterion alone (14).

Finally, it is important to notice that DILI cases diagnosed in tertiary centers are not representative of the whole spectrum occurring in the general population.

Overall, our study emphasizes the relevance of anticancer agents as a cause of DILI. **In an hospital setting, a closer collaboration between oncologists and hepatologists would most likely improve the diagnosis and management of patients with DILI.**

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Table 1. Baseline characteristics of patients (all) by hospital admission or not

Characteristics	N=76	Hospital admission (n=39) 51%	No admission (n=37) 49%	p
Age (years)	58 (42-65)	48 (38-59)	56 (34-65)	0,02
BMI	24(22,3-27,3)	24(22-27)	24(21-28)	0,94
Gender				
Male	44(58%)	22 (56%)	22 (59%)	0,79
Comorbidity				
Diabetes mellitus	3(4%)	0 (0%)	3 (4%)	0,11
Alcohol Consumption	22(29%)	11 (28%)	11 (30%)	0,57
Tobacco use	17(22%)	12 (31%)	5 (14%)	0,07
Previous liver disease	3(3%)	2 (5%)	1 (3%)	0,30
Liver test (Median-IQR)				
ALT (IU/L)	1723 (392-2994)	1892 (561-3439)	431 (225-636)	<0,01
AST (IU/L)	1509 (310-1747)	1368 (481-2321)	199 (134-365)	0,03
GGT (IU/L)	158 (69-259)	171(93-294)	154(78-291)	0,50
ALP (IU/L)	176 (126-232)	213(138-244)	195(131-259)	0,43
Bilirubin (mg/dl)	16,9 (12-20,7)	17,7(12,4-20,5)	1,5(0,4-4,7)	<0,01*
INR	1,41 (1,16-1,76)	1,53(1,3-2,40)	1,02(0,9-1,1)	<0,01
Leucocytes (10 ⁹ cel/l)	6,3 (5,3-9,1)	7,6(5,6-8,5)	6,0 (3,5-7,4)	<0,01
Eosinophils (%)	2,4(1,35-3,0)	1,6(0,7-3,3)	2,1(0,9-3,8)	0,40
Gamma-globulin(g/L)	18,4 (16,75-26,55)	21,0(15,8-25,3)	15,8(12,5-18,2)	0,05
Liver injury pattern				0,13
Hepatocellular	55 (72%)	32 (82%)	23(62%)	
Cholestatic	10(13%)	4(10%)	6 (16%)	
Mixed	11(15%)	3 (8%)	8(22%)	
Clinical features				
Fever	8(11%)	4(10%)	4(11%)	0,94
Skin rash	5(7%)	5(13%)	0(0%)	0,03
RUCAM score	8(6-9)	8,04	8,19	0,73
Drugs:				0,01
Anticancer	20 (26%)	2 (5%)	18 (49%)	
Antibiotics	18 (24%)	15 (38%)	3 (8%)	
Analgesic	9 (12%)	6 (15%)	3 (8%)	
Recreational drugs	7 (9%)	7 (18%)	0 (0%)	
Autoantibodies				0,43
ANA positive	20 (28%)	14 (50%)	6(38%)	
Anti SMA positive	24 (32%)	15 (54%)	9(50%)	0,86
Anti LKM positive	0 (0%)			
Outcomes				<0,01
LT or death	7 (9%)	7 (18%)	0 (0%)	
Resolution	69(91%)	32 (82%)	37 (100%)	
Severity				<0,01
Mild	31(41%)	4 (10%)	27 (73%)	
Moderate	23(30%)	13 (33%)	10 (27%)	
Severe	15(20%)	15 (39%)	0%	
Fatal	7(9%)	7 (18%)	0%	

Quantitative variables are expressed as median (interquartile range) and qualitative variables as numerical (percentage).

BMI: Body Mass Index ANA: Antinuclear Antibodies, SMA: Smooth muscle antibodies, LKM: Liver Kidney microsomal. LT: Liver transplantation. / The normal value for liver test parameters: ALT, AST& GGT (5-40 IU/L) ALP (46-116 IU/L). Total Bilirubin(<1.2 mg/dl) / * Bilirubin remained as a independent factor associated with hospital admission OR 1,2 (1,0-1,4); p=0,04.

Table 2 Outcomes and liver injury pattern by type of drug.

Number of Patients	Drug	Type drug	Liver injury pattern	Outcome admission	Outcome final
9	Amoxicillin-clavulanate**	Antibiotic	7 Hepatocellular 1 Cholestatic 1 Mixed	8 Hospitalization 1 Outpatient	7 Resolution 2 Liver Failure
4 1	Nivolumab* Nivolumab-Ipilimumab*	Anticancer (ICIs)	2 Hepatocellular 1 Cholestatic 2 Mixed	Outpatient	Resolution
4 1	Isoniazid Isoniazid-Rifampicin	Antibiotic	3 Hepatocellular 1 Cholestatic	Hospitalization	Resolution
4	Atorvastatin	Hypolipemiant	1 Hepatocellular 2 Cholestatic 1 Mixed	Outpatient	Resolution
3 1	Cocaine Cocaine-methamphetamine	Recreational Drug	Hepatocellular	Hospitalization	3 Resolution 1 Liver failure
4	Metamizole	Analgesic	Hepatocellular	Hospitalization	3 Resolution 1 Liver Failure
2	Imatinib	Anticancer (PKI)	Hepatocellular	Outpatient	Resolution
2	Pembrolizumab*	Anticancer (ICIs)	Cholestatic	Outpatient	Resolution
1 1	Cyclophosphamide Cyclophosphamide-cytarabine	Anticancer	Cholestatic	Outpatient	Resolution
2	Gilteritinib	Anticancer (PKI)	1 Hepatocellular 1 Mixed	Outpatient	Resolution
1 1	Naproxen Naproxen/meloxicam**	Analgesic	2 Hepatocellular	Hospitalization	Resolution
2	Amphetamines	Recreational Drug	Hepatocellular	Hospitalization	Resolution
2	Disulfiram	Anticraving agent	Hepatocellular	Hospitalization	Liver Failure

1	Futibatinib	Anticancer(PKI)	Hepatocellular	Outpatient	Resolution
1	Ribociclib	Anticancer(PKI)	Hepatocellular	Outpatient	Resolution
1	Encorafenib-Binimetinib	Anticancer (PKI)	Hepatocellular	Outpatient	Resolution
1	Oxaliplatin-fluorouracil	Anticancer	Mixed	Outpatient	Resolution
1	Ibrutinib	Anticancer (PKI)	Hepatocellular	Outpatient	Resolution
1	Durvalumab*	Anticancer (ICIs)	Mixed	Outpatient	Resolution
1	Exemestane	Anticancer	Mixed	Outpatient	Resolution
1	Minocycline	Antibiotic	Hepatocellular	Outpatient	Resolution
1	Sulfamethoxazole-trimethoprim	Antibiotic	Hepatocellular	Outpatient	Resolution
1	Azithromycin	Antibiotic	Hepatocellular	Hospitalization	Resolution
1	Levofloxacin	Antibiotic	Mixed	Hospitalization	Resolution
1	Diclofenac	Analgesic	Hepatocellular	Hepatocellular	Resolution
1	Etoricoxib	Analgesic	Hepatocellular	Outpatient	Resolution
1	Ibuprofen	Analgesic	Hepatocellular	Outpatient	Resolution
1	Energy drink	Dietary supplement	Hepatocellular	Hospitalization	Resolution
1	Eslicarbazepine	Anticonvulsant	Hepatocellular	Hospitalization	Resolution
1	Valproate	Anticonvulsant	Cholestatic	Hospitalization	Resolution
1	Quetiapine	Sedative	Hepatocellular	Outpatient	Resolution
1	Atomoxetine	Antidepressant	Hepatocellular	Hospitalization	Resolution
1	Testosterone	Steroid	Hepatocellular	Outpatient	Resolution
1	Triptorelin	Steroid	Hepatocellular	Outpatient	Resolution
1	Estradiol-progesterone	Steroids	Hepatocellular	Outpatient	Resolution
1	Drospirenone	Contraceptive	Hepatocellular	Hospitalization	Resolution
1	Teriflunomide	Immunosuppressant	Hepatocellular	Outpatient	Resolution
1	Anakinra	Immunosuppressant	Hepatocellular	Hospitalization	Liver Failure
1	Infliximab	Immunosuppressant	Hepatocellular	Hospitalization	Resolution
1	Sulfasalazine	Immunosuppressant	Hepatocellular	Hospitalization	Resolution
1	Simvastatin	Hypolipemiant	Hepatocellular	Outpatient	Resolution
1	Allopurinol	Hypouricemic agent	Mixed	Hospitalization	Resolution
1	Olmesartan	Antihypertensive	Hepatocellular	Outpatient	Resolution
1	Low molecular Weight Heparin	Anticoagulant	Mixed	Outpatient	Resolution

ICIs: Immune Checkpoint inhibitors. PKI : Protein kinase inhibitors. LT: liver transplantation. * Indirect DILI caused by immune check point inhibitors **Drug-induced autoimmune like hepatitis: amoxicillin-clavulanate (1), naproxen/meloxicam (1). *** One patient died without liver transplantation that was contraindicated for heavy alcohol consumption.