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TOPIC HIGHLIGHT

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Hepatitis C virus reactivation in cancer patients in the era of targeted therapies

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Abstract

The purpose of this review is to summarize the evidence of hepatitis C reactivation in cancer patients in the era of targeted therapies. Targeted therapies are novel therapeutics frequently used in cancer patients. During treatment with targeted therapies, viral replication is one of the major problems that can occur. The PubMed database, ASCO, and ASCO Gastrointestinal Cancer Symposium abstracts were searched up until September 15, 2013 using the following search keywords: "targeted therapies, rituximab, alemtuzumab, brentuximab, hepatitis, hepatitis C reactivation, tyrosine kinase inhibitors, imatinib, mammalian target of rapamycin (mTOR) inhibitors, everolimus, anti-HER therapies, trastuzumab, pertuzumab, lapatinib, anti-epidermal growth factor receptor therapies, cetuximab, panitumumab, and ipilimumab". Papers considered relevant for the aim of this review were selected by the authors. The data about rituximab-induced hepatic flare in hepatitis C virus (HCV) positive patients is controversial. However, there is the possibility of life-threatening hepatic flare that can develop after HCV ribonucleic acid (HCV-RNA) viral load increases. Routine follow-up of liver function tests should be advised. Especially in high-risk patients, such as those with baseline chronic active hepatitis and cirrhosis, and where there are plans to administer rituximab concomitantly with corticosteroids, it is advised to have close follow-up of HCV viral load. The data is insufficient to make accurate statements about the association of alemtuzumab therapy and HCV reactivation. However, alemtuzumab may cause deep immunosuppression. Due to this, it is better to follow up with liver function tests and HCV RNA levels during alemtuzumab therapy. Brentuximab has effects on antibody dependent cellular toxicity and may decrease humoral immunity. Thus, we believe that during brentuximab treatment of HCV infected patients, clinicians may encounter hepatitis C reactivation. There have been no reported cases of hepatitis C reactivation with imatinib therapy. However, there are many reports of hepatitis B reactivation with imatinib treatment. Based on the evidence of hepatitis B reactivation with imatinib and the effects of imatinib on immune system functions, we suggest that imatinib therapy might be a risk factor for HCV reactivation. Anti-human epidermal growth factor receptor 2 therapies are not associated with hepatic flare in HCV infected patients. Post-transplant studies reported that mTOR was safely administered to patients with active hepatitis C without causing hepatic flare. Cetuximab and panitumumab have not been associated with HCV reactivation. Two cases of HCV infected melanoma were safely treated with ipilimumab without any HCV reactivation or hepatic flare. Targeted therapies are a new and emerging area of oncology treatment modalities. While treating HCV infected cancer patients, clinicians should be mindful of the immunosuppressive properties of targeted therapies. Further randomized trials are needed to establish algorithms for this issue.

Key words: Hepatitis C; Hepatitis C reactivation; Monoclonal antibodies; Cancer, Rituximab

Core tip: During treatment with targeted therapies, especially with monoclonal antibodies, viral replication is one of the major problems for cancer patients. Especially in high risk patients, such as patients with baseline chronic active hepatitis and cirrhosis, and where there are plans to administer rituximab concomitantly with corticosteroids, it is advised to have close follow-up of hepatitis C virus (HCV) viral load and to perform liver function tests. During alemtuzumab therapy we also advise to follow liver function tests and HCV RNA levels. In the course of imatinib therapy, clinicians should follow liver function alterations. Anti-human epidermal growth factor receptor 2, anti-epidermal growth factor receptor, and immunomodulating therapies can be safely used in HCV positive patients.

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INTRODUCTION

Viral hepatitis reactivation is one of the major challenges encountered during a variety of chemotherapy treatments. In the literature, there is a well-established association between hepatitis B virus (HBV) reactivation and some anti-cancer drugs, especially monoclonal antibodies[1-5]. On the other hand, there is limited data concerning the reactivation of hepatitis C virus (HCV) with chemotherapeutic drugs and targeted therapies. In this review, we aimed to outline the evidence of hepatitis C reactivation in the era of targeted therapies.

Currently, many oncologists encounter patients treated with chemotherapy regimens consisting of targeted therapies. Therefore, it is important to deal with the side effects of these therapies. During treatment with targeted therapies, especially monoclonal antibodies, viral replication is one of major problems for cancer patients. The reactivation of hepatitis viruses has potentially fatal complications, which have to be followed closely and carefully. HBV replication is strongly associated with anti-cluster of differentiation 20 (CD20) monoclonal antibody containing chemotherapy regimens. However, only a few studies have investigated the occurrence of HCV reactivation during immunosuppressive treatments. As we know from the data of transplant patients, HCV RNA negative solid organ transplants did not demonstrate HCV replication in plasma, liver, or peripheral blood mononuclear cells with long-term immunosuppressive treatment[6]. Hepatitis is described as more than a threefold increase in the upper limit of normal serum alanine aminotransferase (ALT) levels on two consecutive examinations. Most chronic hepatitis C patients have stable HCV RNA levels over a long time period, which may be altered no more than 0.5 logs. In this context, hepatitis C reactivation can be defined as an increase of HCV-RNA viral load greater than 1 $\log_{10}$ IU/mL and/or at least a threefold increase in serum ALT in HCV infected patients[7,8].

Hepatitis C virus is one of the leading causes of chronic hepatitis, cirrhosis, and hepatocellular carcinoma[9]. There has been a widely accepted theory related to HCV replication with immunosuppressive treatment[10,11]. According to this theory, hepatitis C reactivation with immunosuppressive therapy can be divided into three phases. In the first phase, an increase in HCV replication in hepatic cells causes cell-mediated immunoreactions. After discontinuation of treatment, the immune system is fully restored. In the third phase, called the recovery phase, liver functions recover and HBV markers return to baseline levels[12]. We will discuss the issue of HCV reactivation according to subtypes of targeted therapies in the section below.

MONOCLONAL ANTIBODIES AGAINST CLUSTER OF DIFFERENTIATION

Rituximab

Rituximab is a chimeric mouse-human antibody that reacts against CD20 antigens expressed on pre-B and mature lymphocytes. By causing B cell depletion, rituximab induces humoral immunity dysfunction, may affect T cell activation, and can also cause dysfunction of cellular cytotoxicity[13]. Rituximab was the first monoclonal antibody approved by the Food and Drug Administration, and is the most widely used treatment for CD20 positive B cell lymphoma patients[14]. As a result of rituximab treatment, B cell depletion occurs within 24-48 h following the first infusion. After completion of rituximab therapy, nearly 6-9 mo are needed for B cell recovery. This may render patients at a high risk of infection. In many studies, it has been demonstrated that HCV infected B cell lymphoma patients had more frequent hepatitis than non-infected controls[15]. In contrast, some studies showed only an increased HCV viral load, but not concomitantly increased liver function tests. One of these reports, by Aksoy *et al*[16], evaluated a case of a HCV infected non-Hodgkin lymphoma (NHL) patient treated with rituximab monotherapy for three consecutive weeks. During rituximab therapy, HCV RNA viral load gradually increased without a significant increase in liver function tests[16]. In another study, the researchers monitored HCV-RNA levels of five HCV-antibody (ab) positive NHL patients treated with rituximab. They observed an increased HCV RNA viral load during and after chemotherapy in all five patients, but only one had a significant increase in liver function tests[17]. In a study from Italy, 156 consecutive HCV infected patients with NHL were retrospectively evaluated. None of the patients had antiviral therapy. In this retrospective cohort, thirty-five patients were administered

rituximab-containing regimens. Five out of thirty-five patients had a mild increase in liver function tests, which did not cause therapy interruption[18].

Nosotti *et al*[19] showed that HCV infected NHL patients had hepatic flares while treated with regimens containing rituximab. In this study, ALT and bilirubin were monitored every 2 wk and monthly for at least 12 mo after completion of chemotherapy, and HCV RNA was monitored every month in HCV positive NHL patients. Hepatic flare is defined as a 5 fold increase according to the criteria of National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0. HCV-positive patients had a 12 fold relative risk of developing liver dysfunction compared to a HCV-negative group ($P < 0.001$). Patients who did not receive rituximab did not develop liver dysfunction. Some patients had hepatic flares during therapy ($n = 3$) and two others had flares after completion of therapy, which may be a consequence of different mechanisms of hepatic damage. Three patients had concurrently increased ALT and HCV RNA, whereas 2 patients showed a HCV RNA increase before the rise of ALT. Hepatic flares in this study did not develop into a clinically important problem and none of the patient treatment regimens were stopped or changed due to liver dysfunction[19]. In a trial by Nosotti *et al*[19], no correlation was found between increased ALT and HCV RNA during hepatic flares. Besides hepatitis B and C, rituximab containing regimens may cause reactivation of many viral diseases, such as cytomegalovirus, parvovirus B19, echo virus, and varicella-zoster virus[20]. On the other hand, in the cohort of Ennishi *et al*[17], only one case had elevated liver enzymes with rituximab therapy. In this case, while liver function tests increased, HCV RNA levels decreased. This suggests to us that the cause of liver damage was an immune reaction against hepatocytes with HCV. This study could not demonstrate any association between increased viral load and hepatic dysfunction[17]. In one single center experience, 4 patients infected with HCV with a diagnosis of NHL were treated with rituximab containing regimens. HCV-RNA and HCV antibody titers were analyzed. They found that after post-rituximab administration, HCV IgG antibodies in all four patients decreased slightly throughout the clinical course. Rituximab induced B cell depletion for many months, but HCV RNA load did not remain elevated. As a result, we think that B cell depletion was not the only reason for the elevated HCV RNA level. Data about the pathogenesis of rituximab induced HCV reactivation is controversial. As a consequence of B cell depletion, IgG antibody titers decrease, which may lead to viral evasion from the immune system and cause accelerated viral replication[21]. Another explanation was obtained from lupus studies. One lupus study demonstrated that regulatory T cells increased within 30 d of rituximab administration, but after the 30th day T cell apoptosis suddenly increased and the number of T cells decreased within 90 d[22]. Decreased numbers of T cells suggest that this decreased amount may have not been enough for suppression of HCV. On the other hand, another study from Italy did not find any association between rituximab administration and HCV reactivation[18]. A third explanation for the association between HCV reactivation and rituximab therapy is that HCV particles are carried by B-lymphocytes of HCV infected patients and after destruction with rituximab these particles disperse to the whole body[23]. In another study, 104 consecutive patients with NHL, who had no antiviral treatment, were retrospectively evaluated. This study aimed to evaluate the liver related effects of rituximab on HCV-infected NHL patients. All patients were screened for HCV serum antibodies. HCV antibody positive patients were further examined for HCV RNA levels and HCV genotyping. Nine out of 104 patients were HCV positive prior to rituximab-containing regimens. Hepatic flare was defined as an ALT increase > 5 times the upper limit of normal. Three of the HCV-Ab positive patients had hepatic flares, as well as a slightly increased HCV RNA viral load compared to HCV-Ab negative patients, none of whom had hepatic flares. The difference was statistically significant ($P < 0.001$). However, no correlation was detected between ALT and levels of HCV-RNA. Until now, there have not been any randomized placebo controlled studies. The results thus far have been from single center institution experiences and small studies. For instance, Dizdar *et al*[24] reported that patients with a high baseline HCV RNA load might have a mortality rate of up to 45% after rituximab containing therapy. The study from Italy evaluated 8 HCV infected onco-hematological malignancies. Seven of the patients had rituximab containing regimens, and all of which had at least a 1.5 log IU/mL increase of HCV RNA level. Hepatic flare was detected after discontinuation of rituximab, possibly due to cell mediated immunological response against HCV infected hepatocytes. One cirrhotic patient had a life threatening hepatic flare[25]. These interesting results were also supported by the results of one cryoglobulinemia patient who had two cycles of rituximab. After discontinuation of rituximab, the hepatic flare observed in this patient coincided with a reappearance of B cells and a HCV RNA decline, suggesting a role of antibody dependent cellular cytotoxicity[26].

In conclusion, the evidence concerning hepatic flare in HCV infected patients undergoing rituximab therapy is inconsistent. However, there is the possibility of life-threatening hepatic flares developing after a HCV-RNA viral load increase. Therefore, routine follow-up of liver function tests should be recommended. Especially in high-risk patients, such as those with chronic active hepatitis and cirrhosis, and where it is planned to administer rituximab concomitantly with corticosteroids and chemotherapy regimens, patients should be closely monitored for HCV RNA levels. For HCV infected lymphoma patients, as suggested in recent studies[27,28], we advise considering anti-hepatitis C virus treatment on an individual basis prior to rituximab therapy.

Alemtuzumab

Alemtuzumab is a human monoclonal antibody against CD52 receptors localized on lymphoid cells[29]. It fixes complements and causes antibody dependent cellular cytotoxicity. Thus, alemtuzumab depletes normal and malignant T and B lymphocytes and causes deep immunosuppression[30]. It can be used alone or in combination with chemotherapy regimens for the treatment of patients with refractory chronic lymphocytic leukemia (CLL) that have poor prognostic factors. In the literature, it was first reported that two CLL patients with occult hepatitis B infection, developed virological and biochemical hepatic flares following alemtuzumab therapy[31]. After publication of the first cases of hepatitis B reactivation with alemtuzumab, the first case of hepatitis C reactivation was reported[24]. This patient in said case was suffering from CLL, and had severe hepatitis due to reactivation of HCV following treatment with a combination of alemtuzumab and methylprednisolone. This was a case of relapsed CLL, which was anti-HCV IgG positive and HCV RNA negative. Liver function tests were within normal limits prior to alemtuzumab therapy. Thirty-four days after the first dose of alemtuzumab and prednisolone, a rapid rise of ALT and gamma glutamyltransferase was detected. Concurrently, HCV RNA viral load increased to $> 10^6$ copies/mL. Immediately after discontinuation of alemtuzumab therapy, administration of ribavirin 600 mg orally twice daily and interferon alfa-2a 180 mcg subcutaneously once weekly was begun. However, HCV RNA copies continued to fluctuate and never returned to normal levels[32].

In conclusion, the data is insufficient to offer clear advice concerning the effect of alemtuzumab therapy on HCV infected lymphoma patients. However, as alemtuzumab causes deep immunosuppression, like all other immune response modifiers during alemtuzumab therapy of HCV infected patients, we advise following liver function tests and HCV RNA levels.

Brentuximab

Brentuximab vedotin is another monoclonal antibody against CD30 on lymphocytes, conjugated with the anti-microtubule agent monomethyl auristatin. CD30 can be found on malignant lymphoid cells and activated T cells. CD30 has an important role in developing memory and effector $CD4^+$ T cells, but its effects on B cells are controversial. However, studies on mice demonstrated that CD30L/CD30 interactions cause an increased humoral immune response[33]. Following binding to CD30, brentuximab vedotin is rapidly internalized and leads to cell cycle arrest and apoptosis. Brentuximab has been used in relapsed/refractory Hodgkin lymphoma and CD30-positive lymphoproliferative disorders[34]. In the literature, there have been no reported cases of viral hepatitis reactivation with brentuximab treatment, but brentuximab may affect antibody dependent cellular toxicity and may decrease humoral immunity. Thus, we believe that during brentuximab treatment of HCV infected patients, clinicians may encounter hepatitis C reactivation. For further comments on this issue, we will have to wait for an accumulation of experience with brentuximab administration.

TYROSINE KINASE INHIBITORS

The tyrosine kinase inhibitor group consists of many different drugs. Some tyrosine kinase inhibitors, especially sunitinib, sorafenib, and pazopanib, still have no reported association with viral hepatitis reactivation in the literature. In a phase 3 trial, sorafenib or sunitinib was administered to hepatocellular carcinoma patients. In this study most of the patients were HBV or HCV positive prior to diagnosis of hepatocellular carcinoma. During treatment, only one patient (0.2%) in the sunitinib arm and three (0.6%) in the sorafenib arm had hepatic failure. HCV and HBV infected patients safely used sunitinib or sorafenib without clinically significant hepatitis C reactivation[35]. However, sorafenib-induced liver failure has only been reported in two patients with a diagnosis of thyroid cancer[36,37]. Although hepatic failure associated with sorafenib treatment is rare, in HCV infected patients the possible development of sorafenib induced hepatic flare must be kept in mind. On the other hand, HCV uses some tyrosine kinase pathways during the replication process[38]. Therefore, some TKIs may have a suppressive role on HCV replication. For example, one *in vitro* study demonstrated that sorafenib efficiently blocks HCV replication *in vitro*[39].

Pazopanib is another multikinase inhibitor used in the treatment of advanced renal cell cancer and different types of sarcomas. In a phase 3 trial of pazopanib in advanced renal cell carcinoma patients, the most commonly detected laboratory abnormality was elevated ALT and AST. However, most of the elevations in liver function tests were asymptomatic and irreversible[40]. There have been no reported cases of hepatitis related to axitinib treatment[41]. We therefore believe that pazopanib and axitinib can be safely used in HCV infected cancer patients. Crizotinib is a novel multi-targeting tyrosine kinase inhibitor. One case report showed acute hepatitis with crizotinib therapy in a dose dependent manner[42]. From this point of view, we should keep in mind that in HCV infected patients crizotinib induced liver injury may cause a high risk of mortality. We will focus on imatinib, which was reported in the literature as causing viral hepatitis reactivation.

Imatinib

Imatinib mesylate is a well-known tyrosine kinase inhibitor of the BCR-ABL fusion gene product, and is generally used for the treatment of chronic myeloid leukemia (CML) and gastrointestinal stromal tumors. Still, there has been no reported case of hepatitis C reactivation under imatinib therapy. However, there were many reports of hepatitis B reactivation in CML patients[43-46]. Interestingly, in none of the gastrointestinal stromal tumor patients was it reported that they had viral hepatitis

B reactivation. Except for CML, only one case of desmoid tumor had hepatitis B reactivation during imatinib treatment. The reason imatinib induces reactivation is unclear, but *in vitro* studies have shown that imatinib can inhibit T-cell activation and proliferation[47]. The explanation is that there is an impairment of differentiation of progenitor stem cells to dendritic cells by imatinib, and as a consequence there is a defective immune response[48]. Two of the reported cases by Lai *et al*[46] support the hypothesis of the immune restoration stage of HBV reactivation. Clinicians should follow up HBV DNA and liver function tests of HBV infected patients during imatinib treatment. There has been no clear data about hepatitis C reactivation. Only one case report has shown that a HCV-positive CML patient with molecular remission did not develop any clinically important hepatic flare[49]. In a phase Ⅱ study, HCV and HBV infected hepatocellular carcinoma patients were treated with imatinib and no clinically relevant hepatic flare occurred as a treatment complication, although one patient had grade 3 ALT elevation in this study. In this trial, imatinib was safely used in HCV and HBV infected patients[50]. These data are insufficient to make a correct interpretation, but based on the evidence of hepatitis B reactivation with imatinib and the effects of imatinib on immune system functions, we think that imatinib therapy might be a risk factor for HCV reactivation in infected patients. Therefore, during imatinib treatment of HCV infected patients, clinicians should be alert and carefully following liver function alterations.

MAMMALIAN TARGET OF RAPAMYCIN INHIBITORS

The most well-known mammalian target of rapamycin (mTOR) inhibitor is everolimus, which is approved in renal carcinoma, neuroendocrine tumors, and breast cancer. Inhibition of mTOR blocks interleukin 2 and nuclear factor-kappa signaling. Therefore, mTOR inhibitors have anticancer and immunosuppressive properties, which can cause various infections[51]. Teng *et al*[52] reported that activation of the mTOR pathway in HBV infected hepatocytes may feedback suppress HBV surface antigen synthesis. According to this report, mTOR inhibitor therapies may potentially activate HBV replication[52]. In a clinical trial of everolimus, one patient died due to HBV reactivation. In the literature, two patients with renal cell cancer were reported to have hepatitis B reactivation associated with everolimus treatment[53,54]. In a phase 3 study, which investigated the efficacy of everolimus in breast cancer patients, the first case of everolimus-related HCV reactivation was reported[55]. Most of our knowledge about everolimus administration in HCV infected patients is dependent on transplant studies. One such study demonstrated that three recurrent hepatitis C patients after liver transplantation were treated with everolimus as a post-transplant immunosuppressive agent. In this study, none of the patients had hepatitis C progression, and clinical, biochemical, and histological parameters were stabilized[56]. Another post-transplant study also included relapsed HCV infections, and demonstrated that everolimus can be used safely without HCV reactivation in long-term post-transplant patients[57]. Temsirolimus is another mTOR inhibitor used for advanced renal cell carcinoma. It has similar immunosuppressive and anticancer properties as everolimus. The use of temsirolimus may cause immunosuppression and an increased risk of infections[58]. To our knowledge, no case of viral hepatitis reactivation related to the use of temsirolimus has been reported in the literature. Although these are post-transplant studies, we should emphasize that mTOR activity is critical for the anti-hepatitis C virus action of interferon[59]. Therefore, we can speculate that mTOR inhibitors may induce HCV replication in HCV infected patients by blocking mTOR activity.

ANTI-HER-2 AND ANTI-EPIDERMAL GROWTH FACTOR RECEPTOR MONOCLONAL ANTIBODIES

Trastuzumab is a monoclonal antibody against HER-2 (also known as ErbB-2). Single center experience reported the results of 10 breast cancer patients infected with HCV. Among 10 patients who received chemotherapy, two received only trastuzumab and two received combination therapy of trastuzumab and cytotoxic chemotherapy. This study demonstrated no clinically meaningful changes in HCV-RNA viral load or increased liver enzymes in breast cancer patients receiving chemotherapy and/or trastuzumab[60]. One interesting case report had decreased HCV RNA levels with trastuzumab therapy. In this editorial it was suggested that epidermal growth factor signaling might be biologically relevant for HCV[61]. To date in the literature, there has been no report related to pertuzumab and lapatinib associated with hepatic flare in HCV infected cancer patients. In summary, it seems to be safe to administer anti-HER2 therapies to HCV infected patients.

Cetuximab and panitumumab are two monoclonal antibodies against epidermal growth factor receptor (EGFR). Although there has been no association with HCV reactivation, there has been interesting data about EGFR and hepatitis C virus. EGFR has been shown to be important in the entry process for HCV[62,63]. HCV infection has been shown to result in EGFR activation. Lupberger *et al*[64] reported that, in HCV infected patients, IFN-alfa and the EGFR inhibitor erlotinib potentiate the anti-viral effect in a synergistic manner.

IMMUNOMODULATING MONOCLONAL ANTIBODIES

Ipilimumab is a recombinant monoclonal antibody that blocks the action of negative T cell regulator cytotoxic T-lymphocyte associated antigen 4 (CTLA4). Therefore,

Table 1 Association of targeted therapies and hepatitis C virus reactivation

Targeted therapy	Increased HCV viral load	HCV related hepatic flare	Liver function test follow-up	HCV RNA follow-up
Anti-CD antibodies				
Rituximab	Yes, in case series	May cause, further studies are needed	Yes	Yes, especially in high risk patients
Alemtuzumab	Yes, in one case report	Yes, in one case report	Yes	Yes
Brentuximab	No data in literature	No data in literature	No	No
Tyrosine kinase inhibitors:				
Imatinib	HBV reactivation in CML patients, insufficient data related to HCV	No (possibly in HBV infected patients)	Yes (DIH)	No
Sorafenib	No, on the contrary in some cases sorafenib may have a suppressive effect on HCV viral load	No	No (DIH)	No
Crizotinib	US	US	Yes, may cause dose dependent hepatitis	No
Pazopanib	US	US	Yes (DIH)	No
Lapatinib	No	No	Yes (DIH)	No
mTOR inhibitors:				
Everolimus	Maybe (2 cases of HBV reactivation in the literature)	Yes (In phase 3 trial as a side effect)	Yes	No
Anti-Her2 Ab:				
Trastuzumab	No	No	No	No
Pertuzumab	No	No	No	No
Anti-EGFR therapies:				
Cetuximab	US	US	No	No
Panitumumab	US	US	No	No
Immunomodulating Ab:				
Ipilimumab	No (Two cases of HCV infected patients were safely treated)	No	Yes (DIH)	No

Ab: Antibodies; US: Unspecified; DIH: Drug induced hepatotoxicity; HCV: Hepatitis C virus.

ipilimumab causes T cell activation and proliferation. Immune mediated hepatitis is a well-known side effect of ipilimumab treatment. CTLA4 pathways have a role in the exhaustion of HCV specific T cells in HCV infected patients[65]. One of the well-known side effects of ipilimumab is autoimmune hepatitis. However, only two cases of HCV infected melanoma patients have been safely treated with ipilimumab without any HCV reactivation and hepatic flare, and one of these case reports showed decreased viral load during ipilimumab treatment[66,67].

CONCLUSION

Hepatitis C reactivation is one of the major challenges during treatment of HCV infected cancer patients. Targeted therapies are a new emerging area in cancer treatment and may interfere with normal immune system function, leading to reactivation of viral hepatitis. We should consider HCV reactivation during treatment with targeted therapies in HCV infected patients (Table 1).

It is clear that an increased HCV viral load is caused by rituximab therapy in HCV infected patients. However, said increase is not directly associated with hepatic flares. The pathogenesis of rituximab induced hepatic flares needs to be investigated in further randomized studies. However, there is the possibility of having life threatening hepatic flares during and after rituximab therapy. In this context, we strongly recommend close follow-up with liver function tests, especially in patients who have baseline active hepatitis or cirrhosis. In addition, if administration of corticosteroids to patients concomitantly with rituximab is planned, we recommend close monitoring of HCV RNA levels. Anti-HCV treatment should be considered on an individual base before rituximab therapy. Alemtuzumab is another monoclonal antibody against CD52 that can cause deep immunosuppression like all other immune response modifiers. We advise testing of liver function and HCV RNA levels for HCV infected patients receiving alemtuzumab therapy. Brentuximab is an anti-CD 30 antibody and may cause hepatitis C reactivation in HCV infected patients. Further evidence is needed to make comments on brentuximab.

As a group, tyrosine kinase inhibitors do not cause HCV reactivation. However, imatinib mesylate, the most widely-used tyrosine kinase inhibitor, has been associated with HBV reactivation. Based on this information, we think that imatinib therapy might be a risk factor for reactivation of HCV in infected patients. Therefore, clinicians should be alert and carefully follow liver function alterations during imatinib treatment of HCV infected patients. mTOR inhibitors have immunosuppressive properties, but only in one phase 3 study was everolimus related HCV reactivation reported as a side effect. In contrast, post-transplant studies demonstrated that everolimus could be safely used in HCV infected patients. Anti-HER2 and anti-EGFR therapies can be safely used in HCV infected patients. To our knowledge, only two cases of a HCV infected melanoma patient were safely

treated with ipilimumab without any HCV reactivation or hepatic flare.

Targeted therapies are a new emerging area of oncology treatment modalities. When treating HCV infected cancer patients, clinicians should be careful about the immune suppressive properties of targeted therapies. Furthermore, randomized trials are needed to establish algorithms for this issue.

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