# Omacetaxine as an Anticancer Therapeutic: What is Old is New Again

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**Abstract:** Omacetaxine mepesuccinate was originally identified more than 35 years ago and initial studies in chronic myeloid leukemia (CML) showed promising activity. It has also been studied in other hematologic and solid tumors as both a single agent and in combination with other treatments. However, the introduction of imatinib and related tyrosine kinase inhibitors (TKIs) abated the clinical development of omacetaxine as a treatment for CML. The advent of resistance to imatinib and other TKIs in CML patients (often due to the presence of an ABL mutation at position 315) has led to a revived clinical interest in omacetaxine in CML patients who failed TKIs. Here we review omacetaxine's mechanism of action (MOA) as a protein translation inhibitor, how its MOA may translate into activity in treatment of cancers, its potential to eradicate leukemia initiating cells and other cancer stem cells and the potential significance of this activity in clinical practice.

**Keywords:** Omacetacine, protein translation inhibition, chronic myeloid leukemia, leukemia initiating cells, cancer stem cells.

## INTRODUCTION

Omacetaxine mepesuccinate (formerly known as homoharringtonine) was originally identified over 35 years ago as a novel plant alkaloid with antitumor properties. The use of omacetaxine as an anticancer therapeutic has been explored in a wide range of solid and hematological malignancies; however, omacetaxine has not yet been approved for clinical use by the United States Food and Drug Administration. The purpose of this review is to discuss omacetaxine's unique mechanism of action (MOA) and how it might be exploited to treat a variety of cancers.

## OMACETAXINE AS A PROTEIN TRANSLATION INHIBITOR

Omacetaxine was found to be an inhibitor of protein translation early on in the investigation of its MOA. Using purified ribosomes and synthetic mRNAs these initial studies showed that omacetaxine inhibits protein translation by preventing the initial elongation step of protein synthesis via an interaction with the ribosomal A-site [1, 2]. The MOA of omacetaxine differs from other translation elongation inhibitors in that omacetaxine acts only on the initial step of protein translation and does not inhibit protein synthesis from mRNAs that have already commenced translation. This is in contrast to other peptidyl transferase center inhibitors such as cycloheximide and anisomycin that inhibit peptide formation on mRNAs that are actively translated. Recent crystallographic studies have provided a clear structural basis for the inhibition of protein synthesis by omacetaxine [3]. By binding the A-site cleft in the peptidyl-transferase center of the ribosome, omacetaxine inhibits protein synthesis by preventing the correct positioning of amino acid side chains of incoming aminoacyl-tRNAs.

In the past, inhibition of protein translation has been thought to be too general an effect and offer little in the way of selectively targeting cancer cells. As the understanding of the regulation of protein translation has grown however, it has become clear that protein translation is markedly up-regulated in cancer cells and high levels of short-lived proteins involved in cell division and survival are required in many cancer types [4]. Interest in the development of novel protein translation inhibitors has dramatically increased recently. This interest is highlighted by the number of novel compounds targeting various aspects of protein translation in clinical trials in a range of different cancer types [5]. Examples of a number of protein translation inhibitors and their MOA are illustrated in Fig. (**1**).

Protein translation inhibitors are diverse in their MOA and they exhibit different effects on different mRNAs and the proteins they encode. For example, inhibitors of protein translation initiation (such as silvestrol [6]) preferentially inhibit the translation of mRNAs with 5'UTRs that are G/C rich and complex 3-dimensional structures. Some of the proteins encoded by these mRNAs are important factors in cancer cell proliferation and survival (e.g., c-Myc, Mcl-1 and Cyclin D1) and the selective loss of these proteins is thought to be part of the MOA of inhibitors of protein translation initiation. In contrast to inhibitors of protein translation initiation, omacetaxine leads to a general decrease in translation efficiency of all mRNAs independent of the template they encode [7]. Despite this general activity, the short-term effect of omacetaxine on cells is the rapid loss of proteins with short half-lives [7-10]. Interestingly, a number of proteins with short half-lives are encoded by the same cell survival and proliferation mRNAs that possess complex 5'UTRs described above (e.g., c-Myc, Mcl-1 and Cyclin D1) and the loss of these proteins appear to be integral to omacetxine's MOA.

One of the key effects of omacetaxine is the rapid loss of c-Myc protein and the consequent down-regulation of c-Myc responsive genes. Of particular note in the context of the current discussion, is the transcriptional regulation of protein translation machinery by c-Myc as c-Myc is part of a feed forward loop whereby increased expression of c-Myc protein promotes expression of elongation initiation factor 4F (eIF-4F) proteins and promotes translation of mRNAs that possess complex 5'UTRs (which includes c-Myc). This feed forward loop is thought to be part of the mechanism by which c-Myc up-regulation leads to tumorigenesis [11, 12]. As c-Myc is preferentially lost from cells treated with omacetaxine, levels of mRNAs encoding eIF-4F proteins are likely to be rapidly reduced (i.e. <4 hours) and augment the direct effects of omacetaxine via this indirect down-regulation of protein translation initiation.

## OMACETAXINE IN CHRONIC MYELOID LEUKEMIA AND OTHER CANCERS

Protein translation in Bcr-Abl positive cells is up-regulated via Bcr-Abl mediated activation of phosphoinositide-3-kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) signaling pathways. Activation of mTOR in Bcr-Abl positive cells leads to phosphoryla-

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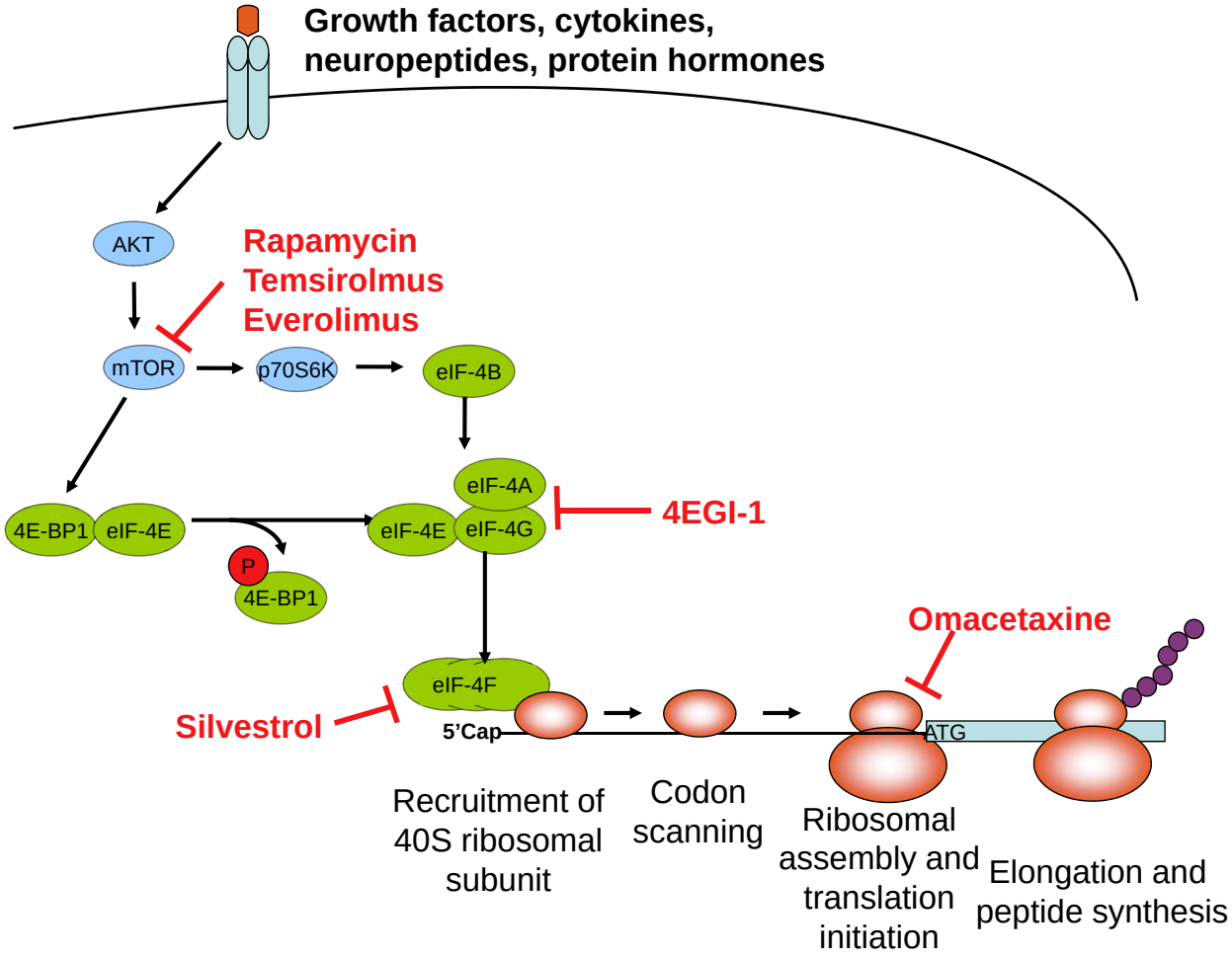


**Fig. (1)**. Mechanism of action of current and future protein translation inhibitors. Abbreviations, 4E-BP1, 4E binding protein 1; EIF, eukaryotic translation initiation factor; mTOR, mammalian target of rapamycin; P, phophorylated; p70S6K, ribosomal protein S6, 70kDa, polypeptide 2.

tion of S6 kinase and 4E-binding protein (4E-BP), key steps in translation of mRNAs with complex 5'UTRs [13, 14]. *In vitro* experiments have shown that inhibition of Bcr-Abl by the tyrosine kinase inhibitor (TKI) imatinib markedly reduced protein translation initiation. In light of these findings it is perhaps not surprising that imatinib has been found to interact synergistically in causing apoptosis of Bcr-Abl positive cells treated with compounds that interfere with translation directly or regulate protein translation initiation. The agents include omacetaxine [8], the mTOR inhibitor rapamycin [15] and the mitogen activated protein kinase interacting serine/threonine kinase 1 (MNK1)/p90 ribosomal S6 kinase (p90RSK) inhibitor CGP-57380 [16]. Omacetaxine has also been found to reduce Bcr-Abl protein levels in Bcr-Abl positive cells [8, 17]. These studies raise the possibility that the efficacy of current chronic myeloid leukemia (CML) therapy with TKIs may be increased by combination treatment with omacetaxine.

Omacetaxine has been found to induce the rapid loss (<4 hours) of a number of short-lived proteins from a number of cell lines derived from CML, acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL) and multiple myeloma patients [9, 10, 18]. These include Mcl-1, Cyclin D1, c-Myc, X-linked inhibitor of apoptosis (XIAP), β-Catenin and the long isoform of cellular FLICE [FAS-associated death-domain-like interleukin (IL)-1β-converting enzyme] inhibitory protein (c-FLIP$_L$). For example, Mcl-1 is up regulated in all AML classes and mouse genetic models clearly indicate that loss of Mcl-1 is protective against AML [19]. Moreover, clinical data suggest that omacetaxine kills AML cells *in vitro* and this is associated with a loss of Mcl-1 and Phase II clinical trial data suggest that omacetaxine may have clinical benefit in AML patients [20-24]. Similar effect of omacetaxine on Mcl-1 was recently described in CLL [25]. Lastly, omacetaxine was shown to decrease the level of Kit protein by inhibiting its translation, leading to a decreased level of the phophorylated native and mutated proteins [26]. These results suggest a role for omacetaxine in mastocytosis. These short-lived proteins clearly regulate proliferation and cell survival and their loss is likely to be involved in the apoptosis induced by omacetaxine in cells that absolutely require the expression of one or all of these proteins for survival.

The loss of proliferation and cell survival proteins induced by omacetaxine may, however, not be sufficient to induce apoptosis in many cancer types due to the presence of a number of dysregulated survival pathways. The loss of these short-lived proteins may however sensitize cancer cells to the action of other anti-cancer therapeutics. This possibility is highlighted by a recent study by Robert *et al.* [7] showing that combination therapy of omacetaxine and the DNA damaging agent doxorubicin were highly effective in prolonging survival in murine Eμ-myc lymphoma models whilst either agent alone were largely ineffectual. In addition, rational combination therapies may be used to take advantage of the decrease in anti-apoptosis short-lived proteins induced by omacetaxine. For example, cells that express high levels of the anti-apoptotic Bcl-2 family proteins Bcl-2, Bcl-x$_L$ and Mcl-1 are resistant to the Bcl-2/Bcl-x$_L$ inhibitor ABT-737 due to the inactivity of ABT-737 on Mcl-1. Combination therapy of omacetaxine and ABT-737 showed a marked synergistic interaction in CML and multiple myeloma cells due to the reduction of Mcl-1 protein by omacetaxine and inhibition

of Bcl-2 and Bcl-$x_L$ activity by ABT-737 [11, 18]. It is also notable that agents that inhibit transcription (such as flavopiridol and SNS-032) exhibit marked synergistic interaction with omacetaxine in CML and CLL cells [8]. As all three of these compounds lead to a loss of short-lived proteins, this approach may offer mechanistic synergism and may therefore help reduce the frequency of acquired resistance during therapy of patients with these conditions.

Pro-apoptotic signaling by tumor necrosis factor (TNF)-superfamily proteins is inhibited in part by negative regulators such as c-$FLIP_L$ and XIAP. As described above, these short-lived proteins are rapidly lost from cells treated with omacetaxine [9]. As a result, it is tempting to hypothesize that omacetaxine will sensitize cells to the effects of TNF-superfamily proteins such as TNF-related apoptosis-inducing ligand (TRAIL) and TNF-α. This possibility is supported by recent data showing that omacetaxine interacted synergistically with an adenovirus that overexpresses human TRAIL in causing apoptosis of myeloid leukemia cells [27]. In addition, c-$FLIP_L$ is a key negative regulator of spontaneous TNF receptor superfamily activation in cells undergoing cell death (or anoikis) following detachment from the extracellular matrix. Omacetaxine and the translation elongation inhibitor anisomycin were found to preferentially sensitize resistant prostate cancer cells (PPC-1) to anoikis [28]. These findings suggest that omacetaxine may be useful in selectively killing cells that are anchorage independent and have high metastatic potential.

## OMACETAXINE AND LEUKEMIA INITIATING CELLS

Leukemia initiating cells (LICs) are a population of stem cells that are capable of tumor initiation and maintenance of the disease. LICs, in CML, are thought to reside in a population of Bcr-Abl positive cells with characteristics of hematopoietic stem cells. A number of studies have shown that current TKIs do not kill these cells at high frequency but rather cause apoptosis in more differentiated Bcr-Abl positive cells of myeloid and lymphoid lineage (reviewed by Jorgensen, *et al* [29]). As a result, we do not know whether TKIs have the potential to cure CML patients of their disease and the patients relapse in the majority of cases following therapy cessation [30]. Recently, omacetaxine, but not the TKI imatinib, was found to induce apoptosis in Bcr-Abl positive LICs in a mouse model of CML [17]. In addition, experiments using primitive $CD34^+CD38^-$ LICs from CML patients showed that omacetaxine can effectively kill Bcr-Abl positive LICs *in vitro* [31]. These data indicate that omacetaxine induces its effects at least in part by targeting the CML LIC population. This raises the possibility that omacetaxine alone or in combination a TKI (such as imatinib, nilotinib or dasatinib) or cytokines (such as interferon-α) that activate the proliferation of CML LICs and increase their sensitivity to cytotoxic compounds may be used to eliminate these CML LICs.

The reason why omacetaxine targets Bcr-Abl positive LICs, while TKIs do not, is unclear at present. It may be that Bcr-Abl positive LICs require expression of certain short-lived proteins and these are preferentially lost following treatment with omacetaxine but not TKIs. Recent data have shown that omacetaxine induces the rapid (<4hr) loss of the anti-apoptotic protein Mcl-1 from Bcr-Abl positive LICs [31] and this may be sufficient to induce apoptosis in these cells. The loss of another short-lived protein, β-Catenin [a key mediator of wingless-type MMTV integration site family protein (Wnt) signaling], impairs the renewal of Bcr-Abl positive CML LICs and reduces the ability of Bcr-Abl to cause leukemia in CML mouse models [32, 33]. Interestingly, recent screening data from the Broad Institute [34] have found that omacetaxine preferentially kills cells that are dependent upon Wnt signaling. As omacetaxine has been shown to cause the rapid loss of β-Catenin in myeloma cell lines [9], it is tempting to speculate that omacetaxine may cause the loss of Bcr-Abl positive LICs by deleting β-Catenin from this cell population.

Another proposed mechanism of CML LICs' resistance to TKIs is cytokine-dependent activation of anti-apoptotic and pro-mitogenic signaling cascades. The cytokine, IL-3, is responsible for cell survival in CML LICs. A very recent study by Klag *et al* [35] indicates that omacetaxine can induce down-regulation of the beta-subunit of the IL3-receptor in primary stem cell cultures at clinically relevant concentrations (40nM) of omacetaxine, eliminating or reducing the binding sites for IL-3.

## OMACETAXINE AND CANCER STEM CELLS

Cancer stem cells (CSCs) are a population of cells that, similar to LICs described above, are capable of tumor initiation and maintenance of the disease (reviewed in [36]). Epithelial CSCs are relatively rare and exhibit resistance to chemotherapeutic agents compared with other cancer cells. This resistance of CSCs to conventional therapies is thought to be one mechanism by which cancer therapies fail to clear the tumor completely leading to recurrence of the tumor and disease progression. Of note is that epithelial CSCs have mesenchymal characteristics with respect to morphology and expression of cell surface markers. In a recent screen for compounds that specifically target CSCs, Gupta *et al.* [37] found that knockdown of E-cadherin (a marker of epithelial cells) in epithelial HMLER breast cancer cells induced epithelial-mesenchymal transition and an increase in treatment resistant CSCs. In a screen based on this cell line, a number of compounds (such as salinomycin) were found to specifically induce apoptosis in CSCs. These compounds represent a novel therapeutic strategy that may be used to specifically target CSCs and thereby improve therapeutic outcomes. As part of this screening effort omacetaxine was found to selectively kill CSCs [34]. These findings suggest that omacetaxine may be used in combination with other front-line therapies to preferentially deplete CSCs and improve the duration of remission induced by current therapeutic interventions in epithelial cancers such as breast, ovarian and lung cancers.

## OMACETAXINE CLINICAL DEVELOPMENT IN CML AND OTHER HEMATOLOGIC MALIGNANCIES

CML is characterized by the clonal expansion of a hematopoietic stem cell possessing a reciprocal translocation between chromosomes 9 and 22. This translocation results in the head-to-tail fusion of the *BCR* gene on chromosome 22q11 with the *ABL* gene located on chromosome 9q34. Attachment of *BCR* sequences to *ABL* converts Abl to a constitutively active tyrosine kinase. Untreated, the disease is characterized by the inevitable transition from a chronic phase to an accelerated phase and on to blast crisis in a median of four years. CML treatment revolutionized following the introduction of the TKI, imatinib; 95% of patients achieve hematologic remission and 76% achieve complete cytogenetic remission at 18 months. Further, all imatinib-treated patients who achieved major molecular remission, defined as ≥3 log reduction in *BCR/ABL* transcript level at 18 months were progression-free at five years. However, approximately 15% of patients discontinue imatinib treatment due to unsatisfactory outcome, resistance being the most common cause. The most frequent reason (40%-50%) for treatment failure is development of mutations in the Abl kinase domain of Bcr-Abl. Of these mutations, a conversion of the amino acid threonine to isoleucine at position 315 (T315I) is resistant to all currently developed TKIs. These patients are in need of other treatments [38].

Before the development of imatinib, the main treatment for CML patients was interferon α that led to reduction in disease burden and a modest survival benefit compared with other treatments. The limited efficacy of interferon α and a high frequency of intolerable toxicities led to the search and discovery of omacetaxine, an alkaloid derivative from the Chinese yew tree [39]. In initial studies, omacetaxine, as a single agent, was found to induce cytogenetic remission in 31% of interferon-α resistant patients [40] and com-

bining it with interferon α induced cytogenetic responses in 25% of newly diagnosed CML patients [41].

In initial Phase I and II clinical studies, omacetaxine was administered intravenously using short (<6 hour) and continuous infusion schedules. In these initial studies, short term administration was associated with unacceptable cardiac toxicity however multi day (>7 days) continuous infusion regimens were found to be better tolerated and induce greater therapeutic benefit (reviewed in [42]). In more recent clinical trials, omacetaxine was administered subcutaneously twice daily for 14 days with similar efficacy and toxicity profiles as with continuous infusion [43, 44]. Pharmacokinetic studies show that omacetaxine undergoes rapid hydrolysis of the methyl ester in plasma to an inactive metabolite [45] and omacetaxine delivered by either subcutaneous or continuous infusion routes exhibit similar pharmacokinetic profiles [46]. Recent data using preclinical *in vivo* models [47] indicate that omacetaxine shows good bioavailability via oral administration however Phase I data have not yet been reported for omacetaxine delivered via this route.

The success of imatinib and other TKIs has obviated the need for any further omacetaxine studies as a front-line therapy for CML; however, several [48-51] have suggested that combinations of omacetaxine with TKIs either in the front-line or salvage setting could provide synergistic activity, allow temporary or permanent TKI withdrawal, revitalized TKI activity in patients who have previously failed TKI due to mutations and/or to lead to an eventual cure for CML.

Omacetaxine has recently been resurrected as a potential treatment for refractory patients with the T315I mutation [52]. It is also being studied in a more recently recognized area of unmet need [53, 54]: patients who fail multiple TKIs regardless of mutational status. Preliminary data suggest that omacetaxine has utility in TKI resistant CML patients [43, 44] and the drug is currently being evaluated by the FDA at the time of writing this manuscript. Clinical studies have also shown activity of omacetaxine as a single agent or in combination with other therapies in AML [20-24, 46, 55-58], myelodysplastic syndrome (MDS) [59-61] and myeloproliferative neoplasms (MPN) [62]. Questions still remain as to what the correct dose or dosing combinations are most appropriate and whether maintenance and/or sequential therapy with omacetaxine and other therapies may have additional benefit in these cancers and in CML.

## IN SUMMARY

Omacetaxine, compared to other therapeutic agents available today, provides a unique MOA in our fight against cancers. In this review we have described its MOA as a protein translation inhibitor and highlighted preliminary data about its possible effects against LICs and CSCs. Further studies that consolidate these early observations may improve treatment outcomes in CML patients and expand omacetaxine's role to other malignancies such as CLL, AML, MDS, MPN, multiple myeloma and potentially epithelial solid tumors. Finally, an effect against LICs and CSCs could open the door to utilize omacetaxine in combination, sequentially or maintenance treatment strategies with other therapeutic agents in a wide variety of cancers.

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## ABBREVIATION

| | | |
|---|---|---|
| 4E-BP | = | 4E-binding protein |
| AML | = | Acute myeloid leukemia |
| CLL | = | Chronic lymphocytic leukemia |
| CML | = | Chronic myeloid leukemia |
| CSCs | = | Cancer stem cells |
| eIF-4F | = | Elongation initiation factor 4F |
| FLICE | = | FAS-associated death-domain-like interleukin (IL)-1β-converting enzyme inhibitory protein (c-$FLIP_L$) |
| LICs | | Leukemia initiating cells |
| MNK1 | = | Mitogen activated protein kinase interacting serine/threonine kinase 1 |
| MOA | = | Mechanism of action |
| mTOR | = | Mammalian target of rapamycin |
| p90RSK | = | p90 ribosomal S6 kinase |
| PI3K | = | Phosphoinositide-3-kinase |
| TKI | = | Tyrosine kinase inhibitor |
| TNF | = | Tumor necrosis factor |
| TRAIL | = | TNF-related apoptosis-inducing ligand |
| Wnt | = | Wingless-type MMTV integration site family protein |
| XIAP | = | X-linked inhibitor of apoptosis |

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