This case series discusses three cases with uncommon neurotoxicity.

1. Sporadic cases of unusual neurotoxicity lack understanding of pathogenic mechanisms.

2. This case series discusses three cases with uncommon neurotoxicity after receiving ciltacabtagene autoleucel (cilta-cel), a B-cell CAR T-cell therapy for multiple myeloma (MM).

3. Complete resolution of Bell’s palsy after completion of glucocorticoid and intravenous immunoglobulin (IVIG) failed with progressive deterioration in the patient’s condition.

4. Further research is warranted to investigate causes, risk stratification, and treatment of neurotoxicity caused by CAR T-cell therapies and ensure better clinical outcomes.

5. Treatment is multimodal with focus on associated symptoms.

6. Prognosis is favorable, symptoms frequently resolve within weeks or months with treatment.

7. Patients without treatment may have residual symptoms including permanent eye injury.

Introduction

Chimeric antigen receptor (CAR) T-cell therapy shows remarkable response rates in refractory hematologic malignancies. 

Cyclophosphamide release syndrome (CRS) and neurotoxicity remain major adverse events.

Sporadic cases of unusual neurotoxicity lack understanding of pathogenic mechanisms.

This case series discusses three cases with uncommon neurotoxicity after receiving ciltacabtagene autoleucel (cilta-cel). Cilta-cel is a B-cell CAR T-cell therapy for multiple myeloma (MM).

Case Presentations

Case #1 - Progressive Multifocal Leukoencephalopathy (PML):

- A 50-year-old female presented with acute renal failure, hyponatremia, and grade 1 CRS (fever) on Day 13 following cilta-cel infusion.

- Brain MRI was concerning for posterior reversible encephalopathy syndrome (PRES) but absence of any neurological abnormalities.

- The patient was treated with Tocilizumab and dexamethasone with complete resolution of Bell’s palsy after completion of glucocorticoid and IVIG.

Case #2 - Polyneuropathy:

- A 74-year-old male had grade 4 CRS and grade 1 ICANS on Day 7 following cilta-cel infusion followed by resolution of CRS and ICANS on Day 18 with Tocilizumab. Dexamethasone, levetiracetam, and lacosamide were used.

- Electromyography (EMG) and nerve conduction study showed electromyographic evidence for severe, chronic, median neuropathy at the right and left wrists.

- In lieu of unremitting extensive work-up, diagnosis of polyneuropathy as a late side-effect of CAR T-cell therapy was established.

- Supportive care treatment provided.

- Two months later tingling in feet resolved but minimal residual tingling in the hands and face persisted.

- The patient was treated with thiamine, leviteracetam, and lacosamide with complete resolution of Bell’s palsy after completion of glucocorticoid and IVIG.

- Electroencephalogram (EEG) was negative, neurofilament light chain (NFL) levels could help in monitoring and predict rate of loss of neurons in the CNS.

- NFL levels could help in monitoring and predict rate of loss of neurons in the CNS.

- First-line treatment is dexamethasone, but other steroids can be considered.

- Prognosis is favorable, symptoms frequently resolve within weeks or months with treatment.

- Patients without treatment may have residual symptoms including permanent eye injury.

References


Conclusion

- Uncommon presentations of neurotoxicity post CAR-T cell therapy have been described.

- Physiopathology remains unclear and most cases are without abnormality in brain imaging.

- Increased blood-brain barrier permeability and loss of integrity are proposed as possible pathogenic mechanisms.

- First-line treatment is dexamethasone, but other steroids can be considered.

- Antisense prophylaxis is also recommended.

- In B-cell-directed therapies, neurotoxicity develops due to on-target, off-tumor effect on B-cells and presence of BCMA in neural tissue.

- NFL levels could help in monitoring and predict rate of loss of neurons in the CNS.

- Prognosis is favorable, symptoms frequently resolve within weeks or months with treatment.

- Patients without treatment may have residual symptoms including permanent eye injury.
Translation Initiation in Cancer: A Novel Target for Therapy

Funda Meric-Bernstam and Kelly K. Hunt
Department of Surgical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030

Abstract
Translation initiation is regulated in response to nutrient availability and oncogene stimulation and is a critical determinant of cellular growth and cell cycle. Several alterations in translational control occur in cancer. Today's therapeutic options cannot alter the translational efficiency of individual cancer cell populations, thus it is a poor drug target. Changes in the expression or activity of translational machinery can lead to new drug targets. Current translational inhibitors do not alter the traditional expression of critical oncogenic targets, such as Ras and PI3K. New translational inhibitors that target cellular growth and proliferation may provide a useful approach to cancer therapy.

Introduction
The fundamental principle of molecular therapeutics in cancer is to exploit the differences in gene expression between normal and cancer cells for therapeutic advantage. This is accomplished by identifying cancer-specific differences in gene expression at the transcriptional, posttranscriptional, and translational levels. These differences include expression of oncogenes, tumor suppressors, and cell cycle proteins. The ability to inhibit or alter the expression of these molecules provides therapeutic potential.

Basic Principles of Translational Control
Translation initiation is the first step in the process of translational control. Translational control is a complex process that is regulated at several levels. The process of translational control involves the interaction of many different factors, including translation initiation factors, mRNA stability, and microRNAs. The overall goal of translational control is to regulate the expression of proteins in response to changes in the cellular environment.

Regulation of Translation Initiation
Translation initiation can be regulated by alterations in the expression or phosphorylation status of the various factors involved. Key components in translational initiation that may provide potential therapeutic targets include:

- eIF4E
- eIF4A
- eIF4G
- eIF4B
- 4E-BP1
- S6K
- P70S6K
- mTOR
- Akt
- SREBP

These factors are regulated by a variety of mechanisms, including posttranscriptional modifications, protein stability, and protein-protein interactions. Alterations in the expression or activity of these factors can lead to changes in the translation of specific mRNAs, which can affect cellular growth and proliferation.

Translation Initiation in Cancer
Translational control is a critical determinant of cellular growth and proliferation. Changes in the expression or activity of translational control factors can lead to alterations in cellular growth and proliferation. These changes can be used as therapeutic targets.

Molecular Cancer Therapeutics
The expression of translational control factors is regulated by a variety of mechanisms, including posttranscriptional modifications, protein stability, and protein-protein interactions. Alterations in the expression or activity of these factors can lead to changes in the translation of specific mRNAs, which can affect cellular growth and proliferation.

Translation Alterations Encountered in Cancer
Several alterations in translational control factors are commonly encountered in cancer. These alterations include:

- Overexpression of translational control factors, such as eIF4E and mTOR
- Mutations in translational control factors, such as PI3K and Akt
- Alterations in the expression or availability of translational control factors, such as 4E-BP1 and S6K

These alterations can lead to changes in the translation of specific mRNAs, which can affect cellular growth and proliferation.

Individual Variations in mRNA Sequences
These variations in mRNA sequences can lead to changes in the translation efficiency of specific mRNAs, which can affect cellular growth and proliferation.

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Translation Initiation in Cancer: A Novel Target for Therapy

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Abstract

Translation initiation is regulated in response to nutrient availability and oncogenic stimulation in concert with cellular protein-cycling processes. Several alterations in translation initiation occur in cancer cells that can affect translation initiation. We review the alterations that take place after the translation of individual mRNA molecules, which is a key role in cancer biology. Changes in the expression of initiation factors, changes in mRNA stability, and altered translation are all important factors in the regulation of translation initiation. Cancer cells have evolved strategies to promote translation initiation in order to increase protein synthesis and translational efficiency. Our understanding of the regulation of translation initiation in cancer represents an important new strategy to develop therapeutic approaches to target cancer.

Introduction

The fundamental principle of molecular therapeutics in cancer is to identify alterations encountered in cancer, and selected therapies targeting translation initiation to elucidate mechanisms of transcriptional quiescence continues until the embryo reaches maturity. When this is the case, some embryos are non-viable, and many embryos are lost. Among these, the inhibition of poly(A) tail synthesis is an important step in the regulation of translation initiation. Thus, further study is needed to understand the effects of eIF4E on translation initiation.

Regulation of Translation Initiation

Translation initiation can be regulated by alterations in the expression or post-translational modification of the translation initiation factors. In eukaryotic cells, translation initiation is initiated by the binding of the 40S ribosomal subunit to the mRNA at the 5′ end. The ribosome binds to the mRNA through the 5′ cap structure, which is recognized by the eukaryotic translation initiation factor 4E (eIF4E). The eIF4E translation initiation complex is then formed by the assembly of eIF4G, the RNA helicase 1 (eIF4A), and eIF4B, which catalyzes the binding of the 60S ribosomal subunit to the ribosome. The 40S ribosome is then assembled, and the 80S ribosome is formed.

The mTOR Pathway

The mammalian target of rapamycin (mTOR) is a serine/threonine kinase that plays a central role in the regulation of translation initiation. mTOR is a component of two distinct complexes, mTORC1 and mTORC2. mTORC1 is activated by growth factors, such as insulin, and regulates protein synthesis in response to nutrient availability. mTORC2 is activated by growth factors, such as insulin, and regulates actin cytoskeleton remodeling and the response to serum and growth factors.

The eIF4F translation initiation complex is then formed by the assembly of eIF4G, the RNA helicase 1 (eIF4A), and eIF4B. The eIF4F translation initiation complex is then formed by the assembly of eIF4G, the RNA helicase 1 (eIF4A), and eIF4B. Therefore, the eIF4F and eIF4G proteins play a critical role in the regulation of translation initiation. In cancer cells, the eIF4F and eIF4G proteins are overexpressed, and this leads to an increase in protein synthesis and translational efficiency.

RNA Packaging

The poly(A) tail in eukaryotic mRNA is important in enhancing translation initiation. A brief description of these variations and examples of each type of variation follow. The poly(A) tail is important in enhancing translation initiation.

Translation Alterations Encountered in Cancer

The translation of mRNA is altered in cancer cells. Several alterations in translation initiation occur in cancer cells that can affect translation initiation. These alterations include changes in the expression of initiation factors, changes in mRNA stability, and altered translation.

Conclusion

Translation initiation is a crucial process in every cell. However, several alterations in translation initiation occur in cancer cells that can affect translation initiation. Further study is needed to understand the effects of eIF4E on translation initiation.

Acknowledgments

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References


Figure 1. Regulation of translation initiation by signal transduction pathways.

Figure 2. Regulation of translation initiation by signal transduction pathways.

Figure 3. Regulation of translation initiation by signal transduction pathways.

Figure 4. Regulation of translation initiation by signal transduction pathways.

Figure 5. Regulation of translation initiation by signal transduction pathways.

Figure 6. Regulation of translation initiation by signal transduction pathways.

Figure 7. Regulation of translation initiation by signal transduction pathways.
Let’s Talk about Pelvic Exenterations: Counseling Women on Living with the Life-Challenging Physical and Emotional Changes

Irene R. Korcz, PhD, LCSW
Department of Social Work, University of Texas MD Anderson Cancer Center

Abstract

The towering Arch of St. Louis is a metaphor for the learning curve in counseling women about the operative procedures of pelvic exenteration. Many health care professionals do not understand the extent of the surgical procedures. Pelvic exenteration is a radical surgical procedure that is used with some women who have cervical cancer and need removal of the uterus in the body by removing en-bloc all of the internal pelvic viscera. (Brunscheid, 1948). At the time, many doctors in the medical profession objected to the pelvic exenteration surgery on moral and ethical grounds.

Development Of Pelvic Exenteration: The Past as Prologue to the Future

During the first half of the 20th century, Dr. Alexander Brunschwig led the way in developing a broad-spectrum surgical approach for pelvic malignancies. Dr. Brunschwig speculated that cancer of the cervix and endometrium could be eradicated if the entire pelvic cavity (Salom & Penalver, 2003).

In 1948, Dr. Brunschwig was considered an outstanding leader in the newly developing area of gynecological surgery. After performing a series of 552 pelvic exenterations, Dr. Brunschwig published the findings of his research on pelvic exenteration in 1950 (Brunscheid, 1948). It was found that surgical complications were numerous, the operative mortality rate of 23% was considerable, and the 5-year survival rate of 15% was small (Anastasi et al., 1958). The outcome of Dr. Brunschwig’s early research indicates that for patients who underwent the pelvic exenteration operation and survival of those tumors, the option of pelvic exenteration did not offer a significant survival benefit (Paley & Shah, 2000).

Research On Pelvic Exenteration For Recurrent Cancer

Over the past five decades there have been additional advances in patient selection criteria for pelvic exenteration surgery as well as refinement in surgical techniques. These factors have led to a change for the better in outcomes. The most recent institutional statistics now report operative mortality under 5% and a 5-year survival rate of 70% (Paley & Shah, 2000).

Current Research on Pelvic Exenteration for Gynecologic Malignancies

In 2010, surgeons in the Dept. of Gynecologic Oncology at the University of Texas MD Anderson Cancer Center in Houston, Texas, performed 14 total pelvic exenterations for women with gynecologic malignancies. In a current research study on pelvic exenteration for gynecologic malignancy at the MD Anderson Cancer Center, 12 of the 14 patients have consented to participate. The objectives of the study are to determine the types of complications experienced by women who undergo pelvic exenteration and to determine if the number of complications differs by vaginal and bladder reconstructive type (Soliman, 2010). In addition, the objective of this research is to longitudinally assess quality of life, sexual functioning and psychosocial functioning of women undergoing pelvic exenteration for gynecologic malignancies. This study will focus on quality of life issues specific to vaginal and bladder reconstruction (Soliman, 2010).

Types of Pelvic Exenteration Operative Procedures (Cloutier, 2004)

<table>
<thead>
<tr>
<th>Anterior Pelvic Exenteration (APEX)</th>
<th>Posterio Pelvic Exenteration (PPEX)</th>
<th>Total Pelvic Exenteration (TPEX)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primarily includes modified abdominoperineal resection with diverting colostomy.</td>
<td>Primarily includes en-bloc radical cystectomy with urinary diversion and possibly radical reconstructive procedures performed.</td>
<td>Primarily includes radical cystectomy with urinary diversion and possibly radical reconstructive procedures performed.</td>
</tr>
<tr>
<td>Includes abdominal wall reconstruction with diverting ileostomy and possibly radical reconstructive procedures performed.</td>
<td>Includes abdominal wall reconstruction with diverting ileostomy and possibly radical reconstructive procedures performed.</td>
<td>Includes abdominal wall reconstruction with diverting ileostomy and possibly radical reconstructive procedures performed.</td>
</tr>
<tr>
<td>Posterior pelvic exenteration with rectovaginal fistula.</td>
<td>Posterior pelvic exenteration with rectovaginal fistula.</td>
<td>Posterior pelvic exenteration with rectovaginal fistula.</td>
</tr>
<tr>
<td>Postoperative care includes support for both.</td>
<td>Postoperative care includes support for both.</td>
<td>Postoperative care includes support for both.</td>
</tr>
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</table>

Case Studies

Case Study #1

- 55 year old married, white female who lived in Houston, Texas.
- Patient was diagnosed with vaginal cancer in 2009 and underwent radical vulvectomy and radiation.
- Patient was referred for disease recurrence.
- Patient was assessed with radiation and chemotherapy.
- Patient was seen weekly and discharged home after 2 months of radiation therapy.
- During recovery:
  - Loss of control over bowel and bladder functions
  - Anxiety, sadness, grief, depression
  - Adjustment to a changed quality of life
  - Irreparable physical and psychological change
  - Fear of recurrence

Case Study #2

- 69 year old married, white, female who lived in Houston, Texas.
- Patient was diagnosed with cervical cancer in 2009 and underwent radical hysterectomy and radiation.
- Patient was seen weekly and discharged home after 3 months of radiation therapy.
- During recovery:
  - Loss of control over bowel and bladder functions
  - Anxiety, sadness, grief, depression
  - Adjustment to a changed quality of life
  - Irreparable physical and psychological change
  - Fear of recurrence

Potential Postoperative Medical Complications

- During recovery: Surgical complications of wound infection, blood clots, delayed suture healing.
- Within 14 months of surgery: Wound breakdown, fistulas, DVT, obstructed intestines, chronic dehiscence, ureteral stenosis, prostatectomy, or urinary tract infection, renal failure and fistula re-occurrence.
- Other possible long-term complications: Peristomal hernia, prostatomegaly of prostates, and stones with pressure on the bowel, or stone formation, mucous formation in conduit and bowel obstruction.

Potential Postoperative Psychosocial Complications

- Anxiety, depression
- Anger, insomnia, grief, fear about the unknown future
- Fear of loss of social support
- Sexual changes in body image
- Relationship concerns with children, friends
- Changes in body/functional issues of stoma or conduit
- Lack of employment, occupational or money issues
- Decrease in physical and social activities
- Adjustment to a changed quality of life
- Loss of control over bowel and bladder functions
- Fear of recurrence
- Impaired sexual adjustment and self-consciousness due to colostomy, ileostomy, vaginal surgery

Counseling the Patient: Three Phases

1. Pre-Operative Counseling

   - Counseling related to the patient selection process for recurrent pelvic cancer:
   - Type of procedure to be performed: Total pelvic exenteration; anterior or posterior pelvic exenteration
   - Explanation of final colostomy, colostomy, neovagina reconstruction using flaps
   - Informal counseling: Counseling regarding the risks and benefits
   - Detailed counseling regarding procedures and the bodily changes that will occur as a result of the surgery
   - Physical therapy evaluation
   - Assessment of Sexual Functioning
   - Advance Directives

2. Counseling during recovery in hospital:

   - Expressive supportive counseling
   - Coping with emotional feelings and physical changes
   - Home care, recreation, transportation and social support network
   - Discharge planning and Case management services

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