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Article / Artículo

Medical education in times of Artificial Intelligence

La educación médica en tiempos de inteligencia artificial

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The evolution of the human race is the result of many years of incomparable history, it is all based on the hand of changing eras and generations. We were analogical, now we are technological. Although teaching is not a section of this chapter, its digital and technological transformation has advanced, as well as the way youth transformed it, going from basic education to motivations, different behaviors, ways of speaking, dressing, and even clothes, compared to two decades ago.

In today's world, it is essential for those of us who practice medical teaching to understand and adapt to these changes. Our role models were our teachers, grandparents, great-grandparents, and doctors, who left a path laid out. However, we must acknowledge that they became the "old guard generation," from whom we learned medicine, humanitarian values, loyalty, ethics, etc. We have lost those innate leaders, who became our mentors, little by little. At this time, we are facing a new generation of "Millennials" who do not understand a reality without technology, learned and are learning about school development, entertainment, and even their work activities in front of a screen [1].

In this case, artificial intelligence (AI) plays a predominant role in medical education and medical treatment. It has transformed the use of a smartphone with high quality technology for medical diagnostics and treatment. Would you like this to change? What does this situation look like from our society's perspective?

According to Heraclitus of Ephesus, "Change is the only constant." This is evolution second by second, without ignoring that for experts in change, with respect to medical errors, it threatens patient safety. Medical technology has been introduced into the highest level of auxiliaries and administrative work with an exemplary approach. It has also been evaluated for new automation opportunities to putt our environment into operation with a single keystroke, and this is the new form of medicine that goes from the interpretation of images to the surgical act, all using robotics [1,2].

Teaching today is complex, and for some, it is challenging to adapt because there are significant medical simulation laboratories created with AI, which can be difficult to access for those who do not have a university connection. There is already teaching training on the subject, simulations that allow the creation of real scenarios, in addition to assessing competencies and skills, in such a way that it will be advisable in new programs e.g., undergraduate and graduate medicine, to involve AI as part of the academic curriculum [3].

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One of the challenges of introducing AI into medicine is the loss of interaction with the patient, which, while true in certain fields like physical rehabilitation, physiotherapy, and mental health, cannot be completely replaced [3]. Currently, there are chatbots for medical use, patient triads, and professional assistants in clinical research; they are powered by AI and also enable privileges and information. Likewise, changes in information, medical-legal complications, image fabrication, and plagiarism can occur, especially in scientific articles that can be created on digital platforms containing unclassified information that could not eventually be detected by anti-plagiarism systems [4].

In the oncological field, AI is integrated every day in a multimodal way from radiological and histological images and advanced molecular diagnoses. This presents new opportunities for automated learning aimed at reaching precision oncology, which goes beyond genomics and standard molecular techniques. However, organizing information through "big data" and integrating computational methods for analyzing and diagnosing heterogeneous lesions seeks to guide its integration towards biomedical education and research in the near future [5].

In the modality of medical education currently directed by Ramírez Arias, formed in 4 aspects, teaching is maintained using technological tools and interactive presentations. Promoting professionalism without losing sight of professional, humanistic ethics, moderating behavior in the doctor-patient relationship and between health personnel, without contributing to alterations in their dress code: "the doctor must always look like a doctor." Strengthening effective communication, we look for tools in everyday care to communicate directly with the patient, their family and colleagues, with the aim of avoiding disputes regarding the patient's needs. Teachers speak and authorize their students; which is an excellent opportunity to create connections by networking and tutoring in group sessions to discuss clinical cases or simply accessing a laboratory technician's room [1].

On the one hand, the implementation of AI in the future could benefit the automation of processes that enable the interaction between doctor and patient. It could potentially enhance diagnostic accuracy, thus becoming a partner in therapeutic decisions. It is increasingly necessary to make critical and bibliographic reviews on the subject [4]. On the other hand, medicine today is still preventive, predictive, participatory, personalized, and precise; with new objective therapies, personalization and precision are linked to the new evidence-based medicine that requires efficient teaching programs supported by the improvement and dissemination of new knowledge [6].

The practical application of new tools has led to a transformation in medical education, yet it poses the traditional challenges of education. This dynamic interplay between innovation and continuity underscores the evolving nature of medical education, keeping it at the forefront of healthcare.

1. Abbreviations

AI: Artificial Intelligence

2. Administrative information

2.1. Additional Files

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2.2. Acknowledgments

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2.3. Author contributions

Conceptualization, formal analysis, research, drafting of the original draft: Dra. Tannia Rivera Rivera.

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2.5. Statements

2.5.1. Conflict of interests

The author declares no conflicts of interest.

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Case report / Caso clínico

Fibrous bone dysplasia: A case report

Displasia fibrosa ósea: reporte de caso

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ABSTRACT

Introduction: Fibrous bone dysplasia is a bone disease that affects the normal composition of the bone, in any part of the skeletal system, whether it is monostotic or polyostic, causing tumor masses of fibrous connective tissue. At the same time, it encompasses a wide phenotypic spectrum that can vary depending on the age of onset and the affected apparatus, such as endocrinopathies. Regarding its diagnosis, if it only affects a single bone without any other finding, it would only need histopathological confirmation. For its treatment could be surgery, antiresorptive drugs such as zolendronic acid, immunological medications and pain management if required. **Clinical Case:** A 14-year-old boy presents with facial asymmetry in the Internal Medicine department. Diagnostic workshop: In computed axial tomography of the skull, an expansive sclerotic lesion with ground glass density is evident at the level of the upper jaw and right zygomatic region. The pathology report of a biopsy taken confirmed the diagnosis of fibrous bone dysplasia. **Conclusion:** This type of dysplasia is rare, and may have a non-progressive asymptomatic course, or cosmetic changes and exacerbating pain in the progressive stage, which poses a challenge for the patient's diagnosis. Several factors must be taken into consideration to choose the best treatment for the patient. For this reason, it should be studied early for an early therapeutic decision.

Keywords: Fibrous dysplasia of bone, monostotic, maxillectomy, zoledronic acid.

RESUMEN

Introducción: La displasia fibrosa ósea es una enfermedad que afecta la composición normal del hueso, en cualquier parte del sistema esquelético, ya sea de forma monostótica o polióstica, y provoca masas tumorales de tejido fibroso conectivo. A su vez, engloba un amplio espectro fenotípico que puede variar según la edad de aparición y aparatos afectos como las endocrinopatías. En cuanto a su diagnóstico, en caso de que solo afecte a un solo hueso sin ningún otro hallazgo, se necesitaría únicamente confirmación histopatológica. Su tratamiento se basa en la cirugía, fármacos antirresortivos, como el ácido zolendrónico, medicamentos inmunológicos y manejo del dolor en caso de que se requiera. **Caso clínico:** Un adolescente de 14 años acude al servicio de Medicina Interna con asimetría facial. En la tomografía axial computarizada de cráneo, se evidencia una lesión expansiva esclerótica con densidad de vidrio esmerilado en el maxilar superior y la región cigomática derecha. El reporte de patología de una biopsia confirmó el diagnóstico de displasia fibrosa ósea. **Conclusión:** Este tipo de displasia es infrecuente y puede tener un curso asintomático no progresivo, o también presentar cambios cosméticos y dolor exacerbante en la etapa progresiva, lo que representa un desafío en el diagnóstico del paciente. Varios factores deben tomarse en consideración para elegir el mejor tratamiento para el paciente. Por tal motivo, debe estudiarse de manera temprana para su decisión terapéutica oportuna.

Palabras Clave: Displasia fibrosa ósea, displasia fibrosa monostótica, maxilectomía, ácido zolendrónico.

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1. Introduction

Fibrous bone dysplasia is a rare, benign, and congenital pathology that affects the skeletal development of the human body by altering the normal composition of the bone [1]. It has a global prevalence of 1/100 000 inhabitants and comprises 5% of all primary bone tumors [2]. Although its etiology is not clear, post-zygomatic mutations of the GNAS gene, located on chromosome 20, have been identified. They lead to the stimulation of adenylyl cyclase and subsequent overproduction of cyclic adenosine monophosphate with uncontrolled cell proliferation and inadequate differentiation [1,3]. Its clinical spectrum is broad, it could be accompanied by dermatological or endocrinological disorders. The diagnosis is made through clinical history, radiological studies depending on the affected bone, and histopathological investigation. Management focuses on observation, pharmacological use with bisphosphonates and surgical treatment [4,5]. There are very few reports in national medical literature on this benign pathology, which is why its scientific dissemination is considered essential.

2. Clinical case

A 14-year-old male patient arrived at the internal medicine department due to facial asymmetry with size increase of the right side of the face for approximately 5 years, without any other symptoms. He denies any personal pathological or surgical history, with a complete vaccination schedule. Physical examination revealed the previously described facial asymmetry, harmony of the upper and lower extremities, and Tanner Score according to age. The rest of the examination shows no significant findings.

In a tomography of the skull and paranasal sinuses (Figure 1), an expansive sclerotic lesion with ground glass density is evident at the level of the upper jaw and right zygomatic region, which remodels and reduces the size of the respective paranasal sinus.

A radiological series is performed on both hands, backbone, lumbosacral, pelvis and femur with a bone age according to that of the patient, without pathological findings.

In laboratory studies, parathyroid hormone 59.3, LH 4.12, FT4 1.32, TSH 2.93, testosterone 6.12 and vitamin D 28.38 were reported; thus, he received vitamin D3 40 000 IU for 2 weeks and zolendronic acid 4 mg intravenously in a single dose.

An excision of the benign tumor and a Cadwell biopsy of the right jaw was performed. Its microscopic study confirmed the diagnosis of fibrous bone dysplasia.

He was intervened for a right maxillectomy, mesh placement under 3D planning and reconstruction with a temporal flap, without complications. The pathology report revealed a homogeneous whitish-brown mass measuring 7.2 x 5.4 x 4.4 cm and confirmed the previous diagnosis.

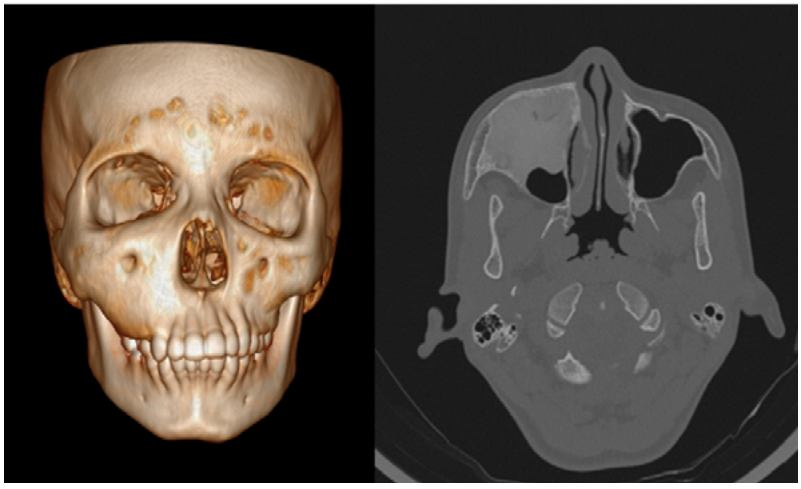

Figure 1. 3D skull tomography and axial tomography of the paranasal sinuses with bone window. Source: SOLCA Hospital – Guayaquil.

Twelve days after the surgical procedure, a new tomographic study of the face (Figure 2) was performed, in which post-surgical inflammatory changes were identified at the level of the surgical bed that extended to the lateral edge and floor of the orbit, as well as the right lateral wall of the orbit, nasal cavity and ipsilateral temporal-parietal region, without evidence of residual lesion and/or recurrence of the tumor.

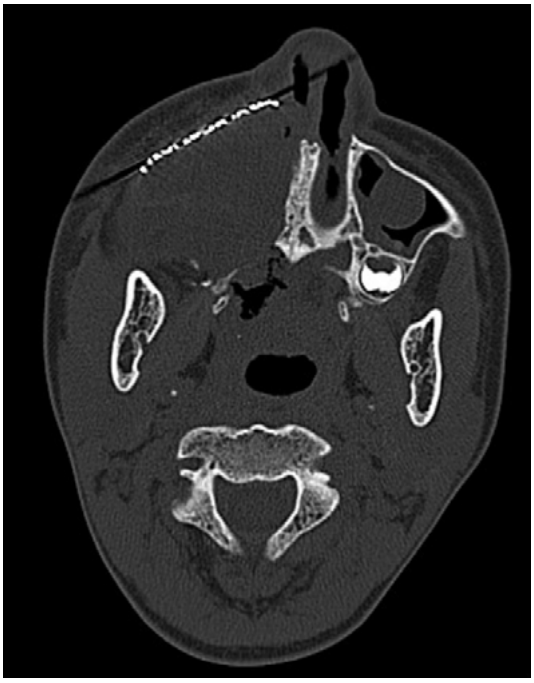

Figure 2. Axial tomography with contrast 12 days after surgery.
Source: SOLCA Hospital – Guayaquil.

Sixteen days after surgery, the patient was evaluated in the outpatient clinic, showing improvement of the facial asymmetry, with a favorable condition.

3. Discussion

Fibrous bone dysplasia is a rare pathology with a wide phenotypic and multi-organ spectrum, whose diagnosis is often challenging in the Internal Medicine field. Also, this condition can affect a single bone (monostotic, as in this case), or several (polyostotic). The former is more prevalent in 70-80% of cases [6,7]. There is no data that determines the prevalence of this disease in Ecuador [8].

Extraosseous manifestations might be associated with café-au-lait macules, hyperthyroidism, acromegaly/gigantism, and abnormal production of testosterone or estrogen, as defined in McCune-Albright syndrome [9,10]; or coexist with intramuscular myxomas in Mazabraud syndrome [1]. During the physical and complementary examinations of this case, none of these alterations were evident.

The diagnostic confirmation of the disease is anatomical-pathological, more reliable for monostotic conditions, since there are several differential diagnoses such as cancer, simple bone cyst, Paget's disease, ossifying fibroma, and giant cell granuloma [1,5,11]. Its malignant transformation is very rare in this type of dysplasia (between 0.4 to 4%) and could help determine polyostotic conditions [12].

Surgery is one of the main treatment options considering the site of the condition and the characteristics of the patient [9]. Various indications for this procedure in craniofacial conditions include compressive neuropathies (such as the optic nerve), severe malocclusion, bone pain resistant to analgesic treatment, high risk of recurrence of the deformity and cosmetic purposes [4,8,13].

Other therapeutic options are bisphosphonates due to their inhibition of bone resorption and decrease of osteoclast production; however, they did not show improvement in radiological findings or in the prevention of expansion of bone lesions [14,15]. Despite this, some intravenous formulations, such as zolendronic acid or pamidronate, have a better therapeutic role compared to the oral route in the treatment of pain related to bone fibrosis [14,16]. Prior to using antiresorptive drugs, it is important to determine the levels of kidney function and calcium phosphorus metabolism (including vitamin D and parathyroid hormone), in case it is necessary to supplement due to deficiencies [3].

Apart from the use of bisphosphonates, another choice includes anti-RANKL antibodies (denosumab) and anti-IL6, which inhibit bone proliferation and reduce pain symptoms, respectively, in case bisphosphonates do not have good efficacy or are contraindicated [15,17].

4. Conclusions

Fibrous bone dysplasia is a benign and rare disease characterized by abnormal growth of bone tissue, which may be accompanied by dermatological and/or endocrinological alterations. Early diagnosis allows for more exhaustive studies and more effective therapy and relief for the patient, highlighting surgical resolution as the first step.

5. Administrative information

5.1 Additional files

None declared by the authors

5.2. Acknowledgements

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5.3. Author contributions

Noemi Bautista Litardo: Conceptualization, methodology, formal analysis, research, project administration, writing of the original draft. **Raúl Peralta Rodríguez:** Conceptualization, Methodology, Research, visualization, writing – review and editing. Both authors read and approved the final version of the manuscript.

5.4. Financing

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5.5. Availability of data and materials

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5.6. Statements

5.6.1. Ethics committee approval

Clinical cases were not needed

5.6.2. Declaration

The manuscript has not been previously published, nor is it currently under editorial review for publication in another journal.

5.6.3. Consent for publication

The patient's legal guardian provided written consent for the publication of this clinical case.

5.6.4. Conflicts of interest

The authors declare no conflict of competence or interest.

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Article / Artículo

Tumor lysis syndrome: review article

Síndrome de lisis tumoral: artículo de revisión

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ABSTRACT

Introduction: Tumor lysis syndrome (TLS) is a potentially lethal complication that originates after the start of cytotoxic chemotherapy. It triggers multiple metabolic alterations due to the rapid lysis of tumor cells and is characterized by symptoms of hyperuricemia, Hyperkalemia, hyperphosphatemia, Hypocalcemia, uremia, and acute kidney injury. **Purpose of the review:** To present the available evidence on tumor lysis syndrome—highlighting those relevant aspects of the topic—to broaden the focus on recognizing it and the guidelines for its prevention and therapeutic management. A bibliographic review was carried out in the electronic databases PubMed, SciELO, and Elsevier; 42 studies and one oncology text published in English and Spanish from 2019-2024 were analyzed. **Relevance:** Early recognition is essential to prevent progression to multiple organ failure. Therapeutic management includes hydration, hypouricemia-lowering agents, and correction of electrolyte imbalance supervised by a multidisciplinary team in a hospital unit equipped for effective patient monitoring. Hemodialysis is the auxiliary therapy in a patient's refractory to medical treatment. **Conclusions:** Given the high mortality due to tumor lysis syndrome, it is essential to identify patients at risk and implement preventive therapeutic measures early, avoiding organic damage.

Keywords: Tumor lysis syndrome, Cancer chemotherapy, Oncology, Cancer.

RESUMEN

Introducción: El síndrome de lisis tumoral es una complicación potencialmente letal que se origina tras el inicio de la quimioterapia citotóxica y desencadena múltiples alteraciones metabólicas por la rápida lisis de las células tumorales. Está representada por cuadros de hiperuricemia, hiperpotasemia, hiperfosfatemia, hipocalcemia, uremia y lesión renal aguda. **Propósito de la revisión:** Presentar la evidencia disponible sobre el síndrome de lisis tumoral —resaltando aquellos aspectos relevantes con relación al tema— para ampliar el enfoque de cómo reconocerlo y las directrices para su prevención y manejo terapéutico. Se realizó una revisión bibliográfica en las bases de datos electrónicas PubMed, SciELO y Elsevier; se analizaron 42 estudios y un texto de oncología, en idiomas inglés y español, publicados en el periodo 2019-2024. **Relevancia:** El reconocimiento temprano es fundamental para evitar el progreso hacia falla multiorgánica. El manejo terapéutico incluye hidratación, hipouricemiantes y corrección del desequilibrio electrolítico, supervisado por un equipo multidisciplinario en una unidad hospitalaria equipada para una monitorización eficaz del paciente. La hemodiálisis es la terapia auxiliar en pacientes refractarios al tratamiento médico. **Conclusiones:** Dada la alta mortalidad por síndrome de lisis tumoral, resulta muy importante la identificación de pacientes en riesgo para iniciar de manera temprana las medidas terapéuticas preventivas y evitar el daño orgánico.

Palabras Clave: Síndrome de lisis tumoral, Quimioterapia, Oncología, Cáncer.

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1. Introduction

The Tumor Lysis Syndrome (TLS) represents a metabolic alteration set. It was first described decades ago after the invention of cytoreductive therapy for the management of neoplastic diseases. It constitutes a true once-metabolic emergency that is seen quite frequently in clinical practice in adult and pediatric cancer patients who undergo therapeutic management with chemotherapy [1, 2].

Cancer constitutes one of the leading causes of morbidity and mortality worldwide, with a variable primary origin, which, added to the mysterious gap in the life cycle of neoplastic cells, generates a wide range of manifestations in the body as a metabolic response [3, 4]. TLS usually appears after the initiation of chemotherapy, although there are reports of spontaneous occurrences in patients with high-grade malignant hematological neoplasms [5, 6].

Since it is a potentially fatal entity, it is relevant to identify those patients with a high risk of presenting TLS. In this way, early recognition of the alterations associated with the timely initiation of therapeutic management is the fundamental pillar to preserve the patient.

This article aims to highlight those relevant aspects of the topic to provide a clearer vision of how to recognize TLS and, with that, the foundations for its prevention and therapeutic management.

2. Materials and methods

2.1 Study design

Descriptive study. A search of scientific literature on the topic was conducted in digital journals published in the last five years in English and Spanish.

2.2 Databases analyzed

To search for information, we used the electronic databases PubMed, SciELO, and Elsevier. These databases allowed us to collect information from scientific articles, systematic reviews, descriptive studies, and literature reviews focused on the topic.

2.3 Search terminology

The search was conducted in English and Spanish using the descriptors: “Tumor lysis syndrome,” “Oncology,” “Cytotoxic chemotherapy,” “Cancer,” obtained from the Descriptors in Health Sciences (DeCS) and “Tumor lysis syndrome,” “Oncology,” “Cytotoxic chemotherapy,” “Cancer” obtained from Medical Subject Headings (MeSH), linked with the Boolean operator AND.

2.4 Inclusion criteria

Scientific articles published in the period 2019-2024 in English and Spanish.

2.5 Exclusion criteria

Duplicate articles or articles unrelated to the topic in languages other than those indicated or published outside the established period.

3. Results

From the total number of studies yielded by the search, 42 articles and one oncology text were selected and analyzed.

3.1 Definition

TLS is defined as an acute, potentially fatal condition in both adults and infants associated with the initiation of cytotoxic therapy in neoplastic treatment [2]. It is characterized by a pattern of metabolic alterations resulting from the massive release of intracellular contents from cancer cells into the systemic circulation. These specific findings include conditions such as uremia, hyperphosphatemia, Hyperkalemia, hyperuricemia, and Hypocalcemia, which together can lead to severe complications such as cardiac arrhythmias, seizures, kidney failure, and even death due to multiple organ failure [2, 8].

3.2 Etiology and risk factors

The presence of TLS is generally recognized in patients suffering from hematological malignancies. It is also common for it to occur in high-grade lymphomas after having started treatment with aggressive chemotherapy. However, solid tumors can also cause TLS, although to a lesser extent. Among them, the most frequent are neuroblastoma and hepatoblastoma. Some data mention that a clinical picture of TLS can spontaneously exist without starting chemotherapy [8, 9].

It has also been considered that the risk of TLS increases in the presence of leukocyte counts greater than 100,000 cells/mm, lactate dehydrogenase twice the normal level, bulky disease (greater than 10 cm), hepatomegaly, splenomegaly, bone marrow involvement, and preexisting kidney disease [10,11].

3.3 Epidemiology

The incidence of TLS is not known with certainty; multiple factors influence its occurrence and development, e.g., a high tumor burden, the presence of neoplasms with a high rate of cell proliferation, and greater sensitivity to cytoreductive therapy. Apart from preexisting kidney disease or rapid deterioration of the patient during their illness, there is no predisposition based on race or sex [10].

3.4 Pathophysiology

TLS is a set of clinical manifestations resulting from metabolic alterations due to the massive release of intracellular ions such as potassium, phosphorus, and uric acid, which in large quantities exceed the kidney's capacity to excrete them [6]. The degradation of nucleic acids produces xanthine as a final product, a compound that, when oxidized, leads to the formation of uric acid. This substantial metabolic load causes the deposition of calcium phosphate crystals, xanthine, and uric acid in the distal renal tubules, collectively resulting in obstructive uropathy and a subsequent decrease in the glomerular filtration rate (GFR), which in turn leads to acute kidney injury (AKI). Factors such as cellular sensitivity to cytotoxic therapy, the efficacy of chemotherapy, underlying renal system dysfunction, dehydration, and urinary acidity create an environment that contributes to the clinical development of TLS [10,11].

Furthermore, there is a premise that uric acid stimulates AKI through mechanisms beyond crystal formation, like renal vasoconstriction, which leads to reduced blood flow to the organ, inflammation, and deregulation of the internal environment. This also results in the overexpression of C-reactive protein and nitric oxide [10, 12].

3.5 Electrolyte Imbalance

3.5.1 Hyperkalemia

Tumor cell lysis causes a massive release of potassium. The liver and skeletal muscles absorb excess potassium, and the remainder is excreted through the renal and gastrointestinal systems. In obstructive uropathy, uric acid salts significantly limit potassium excretion, leading to dangerously high levels and an increased risk of arrhythmias and cardiac arrest [13, 14].

3.5.2 Hyperphosphatemia

Tumor lysis causes the nucleic acids within neoplastic cells to release phosphate groups, which in turn release a higher-than-normal amount into the bloodstream. Since phosphorus is primarily excreted via the kidneys, AKI inhibits the kidney's ability to filter this element. Hyperphosphatemia is more commonly observed in chemotherapy-induced TLS than in spontaneous TLS, and as a result of hyperphosphatemia, calcium chelation occurs, thus leading to Hypocalcemia [15, 16].

3.5.3 Hypocalcemia

It represents a potentially fatal condition that occurs as a secondary effect of hyperphosphatemia. It also leads to complications that require immediate attention due to the risk of mortality, e.g., cardiac arrhythmias, tetany, and seizures [17, 18].

3.6 Histopathology

Findings consistent with deposits of uric acid, xanthine, and calcium phosphate crystals can be found in renal tissue. The factors associated with and contributing to crystal formation include low urine flow, a higher concentration of solutes, and their low solubility in the urinary environment [19, 20].

3.7 Clinical Assessment

Symptoms reveal metabolic alterations that arise approximately 12 to 72 hours after starting chemotherapy or spontaneously without having initiated cytoreductive therapy [21]. It is necessary to consider the primary cause that triggered the clinical manifestations, as well as to identify common symptoms such as anorexia and weight loss. In this case, digestive symptoms include nausea, vomiting, and diarrhea; urinary symptoms include dysuria and hematuria. Notable signs of fluid overload include pitting edema, marked abdominal distension, and facial edema. The presence of vomiting, spasms, muscle cramps, convulsive episodes, tetany, or altered mental status suggests Hypocalcemia. Uremia may manifest as a metallic taste in the mouth, pruritus, abnormal lung sounds due to volume overload, joint pain, uremic pericarditis that muffles heart sounds, and renal colic-like pain. Multiple pathophysiological events may lead to extensive TLS, resulting in multiorgan failure and sudden death [22, 24].

3.8 Diagnosis

The diagnosis can be classified under clinical and laboratory criteria. In this case, it was based on the Cairo-Bishop classification criteria, which include a 25% change from the initial values of uric acid, potassium, phosphorus, and calcium. The diagnosis is determined when two or more criteria are identified within the period from three days before to seven days after the start of cytotoxic therapy [25, 26].

3.8.1 Laboratory Diagnosis

Two or more of the following criteria within 24 hours [10, 25]:

- Uric acid elevation of 25% or ≥ 8.0 mg/dL
- Potassium elevation of 25% or ≥ 6.0 mg/dL
- Phosphate elevation of 25% or ≥ 4.5 mg/dL
- Calcium decrease of 25% or ≤ 7.0 mg/dL

3.8.2 Clinical Diagnosis

Includes a positive laboratory diagnosis plus the presence of at least one clinical criterion [10, 25]:

- Elevated serum creatinine or ≥ 1.5 times the upper standard limit.
- Cardiac arrhythmias or sudden death
- Seizures

When performing imaging studies, it is necessary to be cautious when administering intravenous contrast media due to the presence of AKI in TLS. The electrocardiogram (ECG) is a fundamental part of the patient's evaluation, as it helps detect Hypocalcemia and Hyperkalemia. A complete blood analysis assists in assessing the cellular and metabolic components in the blood; an elevated blood chemistry value could indicate TLS. In urinalysis, analyzing the pH is advisable, as it determines the effectiveness of the treatment regarding urinary alkalinization [2, 10].

3.9 Treatment

Laboratory values should be monitored every 4 to 6 hours initially. Additionally, urine output should be closely observed. Given the need for close monitoring, the patient's admission to the intensive care unit (ICU) should be considered for optimal management [27].

3.9.1 Hydration

The fundamental part of treatment is rapidly expanding intravascular volume with isotonic solutions; crystalloid solutions help increase the glomerular filtration rate (GFR). Intravenous hydration should begin 48 hours before chemotherapy and continue for 48 hours after completion. Approximately 3 to 3.5 liters/m^2 per day are necessary to achieve a diuresis of 80 to 100 ml/hour, or approximately 3 liters daily; this can be supported by using potassium-reducing loop diuretics [27, 28]. It is essential to consider factors such as a history of heart failure [29].

3.9.2 Reduction of uric acid levels:

Allopurinol is a xanthine oxidase inhibitor that can reduce uric acid levels and prevent the development of TLS. Therefore, it is a practical choice for managing patients at risk of TLS and can be used at a dose of 300 mg, with a maximum dose of 800 mg, as long as renal function is preserved. Its effect is achieved after 48 to 72 hours of treatment, which should be administered 2 to 3 days before starting chemotherapy and continued for 10 to 14 days [27, -30]. In cases of hypersensitivity to the drug, febuxostat has shown effective control of TLS-related hyperuricemia in studies with a good safety profile without causing the hypersensitivity reactions associated with allopurinol (eosinophilia, hepatitis, and interstitial nephritis). It is usually administered at a dose of 120 mg [30, -31]

Derived from Aspergillus, recombinant urate oxidase or rasburicase is a drug that, after its metabolism in the body, converts uric acid into allantoin, carbon dioxide, and hydrogen peroxide; allantoin is a metabolite up to 10 times more soluble in urine compared to uric acid [32]. It should be administered between 4 and 24 hours before the start of chemotherapy at a dose of 0.2 mg/kg/day in a 30-minute intravenous infusion for five days and in patients with low risk of TLS, a dose of 0.1 to 0.15 mg/kg [33]. Studies revealed that administering single doses of rasburicase of 6 mg in adults and 0.15 to 1.15 mg in children provides normalization of serum uric acid levels [34]. In contrast, Yaman et al. [35] mention in

their study that a single dose of 7.5 mg effectively controls clinical TLS. It is contraindicated in patients with glucose-6-phosphate dehydrogenase deficiency (risk of methemoglobinemia or hemolytic anemia), pregnant women, and lactating women [36, 37]. It is important to emphasize that its use is limited by its high economic cost [37].

Urinary alkalinization with sodium bicarbonate was a previously recommended method to facilitate uric acid excretion; however, it is no longer recommended due to its ability to promote the precipitation of phosphate and calcium in the kidney tubules, further aggravating AKI in TLS [38, 39].

3.9.3 Correction of Electrolyte Abnormalities

Hyperkalemia, particularly with values above six mmol/L, can be addressed using bicarbonate, polarizing solutions, calcium gluconate, or furosemide [40, 41]. If phosphate levels exceed 6 mg/dL and the patient is stable, treatment can be administered orally with 300-600 mg of aluminum hydroxide [16]. Asymptomatic Hypocalcemia is not treated due to the risk of calcium crystal precipitation in the renal tubules; however, if symptoms are present, it can be managed with 1 gram of calcium gluconate orally. This dose may be repeated until symptoms resolve. Managing hyperphosphatemia helps prevent secondary Hypocalcemia [42]. Hemodialysis is indicated in cases with significantly elevated and potentially life-threatening potassium and phosphorus levels. Continuous renal replacement therapy (CRRT) can prevent rebound hyperkalemia [42, 43].

4. Conclusion

TLS is a potentially fatal hematological-oncological emergency best managed by a multidisciplinary team of professionals, including specialists in oncology, nephrology, internal medicine, intensive care, and the ICU nursing team. Given the delicate nature of this clinical environment, it is essential to identify patients at risk for TLS so that therapeutic management can begin as early as possible. Early recognition of metabolic and renal alterations and timely treatment initiation are crucial for saving the patient's life.

5. Abbreviations

CRRT: Continuous Renal Replacement Therapy

ECG: Electrocardiogram

AKI: Acute Kidney Injury

TLS: Tumor Lysis Syndrome

GFR: Glomerular Filtration Rate

ICU: Intensive Care Unit

6. Administrative information

6.1 Additional files

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6.3 Authors contributions

The author is responsible for conceptualizing the idea, analyzing it, searching it, and writing the manuscript.

6.4 Funding

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6.5 Declarations

6.5.1 Ethics Committee Approval

Not applicable.

6.5.2 Conflicts of Interest

The author declares that there are no conflicts of interest**.**

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Article / Artículo

Disease Free Survival and Overall Survival in Triple-Negative Breast Cancer Patients with Post-Neoadjuvant Residual Disease Treated with Adjuvant Capecitabine

Capecitabine in breast cancer

Supervivencia libre de progresión y supervivencia global en pacientes con cáncer de mama triple negativo con enfermedad residual postneoadyuvancia tratadas con capecitabina adyuvante

Capecitabina en cáncer de mama

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ABSTRACT
Background: The scarcity of effective therapies has contributed to poor outcomes in triple-negative breast cancer. **Objective:** To evaluate overall and progression-free survival in patients with triple-negative breast cancer with post-neoadjuvant residual disease, treated with Capecitabine. **Methods:** Retrospective cohort study. Kaplan-Meier survival functions were calculated. Additionally, Cox regression models were developed for association analysis. **Results:** Forty-one patients were included, of whom 25 (61%) were postmenopausal, 23 (56.1%) had initial tumors ≥5.1cm. The median PFS was 25.03 months (95% CI, 13.37 - 36.68). Twenty six percent of patients had progression at 36 months follow-up, 54.5% of those who had progression were premenopausal. In women with postmenopausal status, higher PFS was observed (HR0.32, 95% CI 0.09 -0.98, p 0.045). The median OS was 55.60 months (95% CI, 46.5-58.5). There was no significant difference between the RCB (Residual Cancer Burden) score and PFS and OS. **Conclusion:** favorable results were observed in patients with post-neoadjuvant residual disease treated with adjuvant Capecitabine, particularly in postmenopausal patients with less previous tumor size.

Keywords: Triple-negative breast cancer, Capecitabine, ARB, residual disease, disease free survival, overall survival.

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RESUMEN

Antecedentes: La escasez de terapias eficaces ha contribuido a que el cáncer de mama triple negativo tenga resultados desfavorables. **Objetivo:** Evaluar la supervivencia global y libre de progresión en pacientes con cáncer de mama triple negativo con enfermedad residual postneoadyuvancia, tratadas con capecitabina. **Métodos:** Estudio de cohorte retrospectiva. Se calcularon funciones de supervivencia de Kaplan-Meier. Además, se desarrollaron modelos de regresión de Cox para análisis de asociación. **Resultados:** Se incluyeron 41 pacientes, de las cuales 25 (61 %) eran posmenopáusicas y 23 (56,1 %) tenían tumores iniciales ≥ 5,1 cm. La mediana de supervivencia libre de progresión fue de 25,03 meses (IC 95 %, 13,37-36,68). El 26,8 % de las pacientes presentaron progresión a los 36 meses de seguimiento, entre ellas, el 54,5 % eran premenopáusicas. En las mujeres con estado postmenopáusico se observó mayor supervivencia libre de progresión (HR 0,32, IC95 % 0,09-0,98, p 0,045). La mediana de supervivencia global fue de 55,60 meses (IC 95 %, 46,5-58,5). No se observaron diferencias significativas entre el score RCB (Residual Cancer Burden) y la supervivencia libre de progresión y la supervivencia global. **Conclusión:** En pacientes con enfermedad residual postneoadyuvancia tratadas con capecitabina adyuvante se observaron resultados favorables, sobre todo en aquellas pacientes postmenopáusicas y con menor tamaño tumoral previo.

Palabras Clave: Cáncer de mama triple negativo, capecitabina RCB, enfermedad residual, supervivencia libre de progresión, supervivencia global.

1. Introduction

Breast cancer is the most common cancer and specific cause of death among women living in Latin America and Caribbean region with 200,000 new cases and more than 52,000 deaths per year (1). It is also located in the first place of incidence for Colombia with 15,509 cases and a mortality of 4,411 cases by 2020 (2). Among all new cases of breast cancer, triple negative breast cancer (TNBC) occurs at a frequency from 15% to 20% (3).

The high heterogeneity, aggressiveness and absence of a receptor that acts as a target for the development of new drugs explain the fact that TNBC is the subtype with the least favorable clinical results and with the smallest number of effective therapeutic options (3).

Although some inhibitors have proven to be effective in the neoadjuvant phase, their high price and not very good cost-effectiveness mean that from the perspective of payers, these inhibitors at their current price will probably not be the choice for patients with TNBC (4). This is why chemotherapy continues to be the cornerstone of treatment, both neoadjuvant and adjuvant. In the neoadjuvant setting, chemotherapy is typically administered with the goal of shrinking the tumor and potentially achieving a better surgical outcome, as well as evaluating the patient's prognosis (5). Currently, the standard chemotherapy for the treatment of TNBC is represented by the sequence of taxanes (docetaxel/paclitaxel) and anthracycline (6-10).

However, even though the chemotherapy regimen is effective, the 10-year risk of relapse of TNBC ranges between 20 and - 40% (11); therefore, it is necessary to explore the role of new chemotherapy agents and regimens to obtain important benefits in the survival of these patients.

Capecitabine is a nucleoside analogue —commonly used in patients with metastatic breast cancer —whose role in the treatment of TNBC has aroused special interest (11,12).

Several studies have analyzed the role of Capecitabine in the treatment of TNBC and obtained heterogeneous results. The CREATE-X study evaluated the role of Capecitabine in relation to DFS in patients with triple negative disease, the DFS rate was 69.8% in the Capecitabine group versus 56.1% in the control group (HR 0 .58; 95% CI, 0.39 to 0.87), and the OS rate was 78.8% versus 70.3% (hazard ratio for death, 0.52; 95% CI, 0.30 to 0.90) (13). The GEICAM/2003-11-CIBOMA/2004-01 study explored adjuvant Capecitabine after standard chemotherapy in patients with early TNBC, but this study failed to show a statistically significant increase in DFS when adding Capecitabine to standard chemotherapy in patients with early TNBC (14).

Considering the contradictory results and the absence of data from Latin American populations on the effect of neoadjuvant Capecitabine in patients with TNBC, it is necessary to provide new evidence that allows drawing conclusions and individualizing treatment options for these patients.

The primary objective of this study was to evaluate the progression-free survival (PFS) of patients with stage I-III triple-negative breast cancer with postneoadjuvant residual disease, treated with Capecitabine,

in an oncology reference center in the city of Medellín. As a secondary objective, overall survival (OS) was evaluated in these patients.

2. Materials and methods

The protocol of this study was approved by the institutional ethics committee for research in human beings of the CES University (cod. Acta211Proy973) and by Fundación Colombiana de Cancerología Clínica Vida (FCCCV). Since this is a retrospective study, without any intervention in the care of the patients, the informed consent used for research studies at the institution was not required. Patient data were guaranteed to be submitted anonymously and confidentially. The reporting of results follows the recommendations of the STROBE guideline (15).

2.1. Design and context

Observational follow-up study of a cohort from April 15, 2018 to April 27, 2023, until death or administrative censorship, based on records taken from the database of the Fundación Colombiana de Cancerología Clínica Vida (FCCCV) of Medellín between 2019 and 2023. Data collection was carried out from February 15, 2023 to May 18, 2023; mortality of all patients was evaluated on June 6, 2023 on the Adres platform (16). The Administrator of the Resources of the General Social Security Health System (ADRES by its Spanish acronym) is the State entity in which the population's records are located, including their date of death.

2.2. Participants

From the information provided by the FCCCV, a total of 144 records of patients who were prescribed Capecitabine at the institution were reviewed. Patients were included in the study if they met the following criteria: women over 18 years of age, with triple negative breast cancer, stage I–III, with residual disease after neoadjuvant chemotherapy, and who received Capecitabine as adjuvant monotherapy. The exclusion criteria were bilateral breast cancer, multiple synchronous cancers, previous treatment with oral Fluoracil, pregnant and lactating patients. Patients whose records had more than 10% of missing data were also excluded.

2.3. Triple negative breast cancer

The triple negative subtype was defined as hormone receptor negativity by immunohistochemistry and Her2 negative by immunohistochemistry (Her2 0 or 1+) or FISH (*in situ* hybridization) test in cases of equivocal Her2 (2+).

2.4. Variables

The primary outcome variable was OS, which was calculated from the time of treatment initiation to the last follow-up or time of death from any cause. PFS was a secondary outcome variable that was calculated from the time of treatment initiation until progression was documented or to the last follow-up without evidence of progression. The initial characteristics of the patients were considered; age, menopausal status, tumor size, axillary lymph node involvement, neoadjuvant chemotherapy regimen received, surgery performed, as well as characteristics of residual disease focused on Residual Tumor Burden (RCB).

2.5. Data sources

The FCCCV IT team was asked for the list of patients admitted between 2019 to 2023 for TNBC, treated with adjuvant Capecitabine, subsequently a review of the medical history of each patient was carried out to determine who met the inclusion criteria and thus obtain the data of interest for the study.

To determine the diagnosis, the date of the first histopathological study was taken. For progression, the date of the first imaging study that showed locoregional or distant change was recorded. Finally, the cut-off date to evaluate survival was June 6, 2023, for all patients by checking their activity status on the Adres platform (16).

2.6. Bias control

Data collection was carried out by a researcher who verified in each clinical record that the inclusion requirements were met and entered them in the corresponding Excel template where each variable of interest was stipulated. In case of doubt about any variable record, it was consulted with expert researchers in the area (mastologist, oncologist or epidemiologist).

The clinical record was initially reviewed, if it lacked information or was incomplete, the mastology evaluations were verified and in cases in which none was available, the data were extracted from the notes of the other specialties related to breast care of the patient due to their oncological condition (pain and palliative care or oncological rehabilitation).

2.7. Statistical methods

A univariate analysis was performed to characterize the study population considering the nature of the variables. In the case of quantitative variables, the Kolmogorov-Smirnov normality test was performed to define whether they presented averages or medians. Qualitative variables were analyzed using absolute and relative frequencies. Median survival was calculated using the Kaplan Meier curve.

For the bivariate analysis, differences in survival according to covariates were calculated by the log Rank test.

A multivariate analysis was performed through the association between covariates and time to event using COX regression. A p value less than 0.05 was considered statistically significant. All analyzes were performed in SPSS version 25.

3. Results

3.1. Participants

A total of 41 patients met the inclusion criteria. With a median age of 55 (44.5-65.5) years old. Of them, 25 (61%) were postmenopausal and only 16 (39%) were premenopausal. The most common histological subtype was invasive ductal carcinoma in 39 people (95.1%). T4b was the most common staging of the patients in 14 (36.6%). The initial descriptive data of the patients are presented in Table 1.

3.2. Response to neoadjuvant chemotherapy and Capecitabine

In 70% of cases, chemotherapy management consisted of the use of doxorubicin (60 mg/m2) plus cyclophosphamide (600 mg/m2) every 21 days with support of granulocyte colony-stimulating factors in each cycle, followed by Paclitaxel (80 mg/m2) weekly for 12 weeks. Only 22% received a regimen with anthracyclines in dense doses (every 14 days) due to access barriers. The use of platinum in neoadjuvant treatment was carried out in 68% of cases in conjunction with paclitaxel.

The most common neoadjuvant chemotherapy regimen was anthracyclic plus taxanes in 36 patients (87.8%), the other regimen used in 3 patients (7.3%) was taxanes plus platinum, as described in Table 1.

In eight patients (19.5%), the pathology of the surgical specimen reported RCB 1, in 20 patients (48.8%) RCB 2, and only 13 (31.7%) reported RCB 3. Table 2 shows the characteristics of the patients after neoadjuvant treatment.

Table 1. Baseline characteristics of patients with triple-negative breast cancer with postneoadjuvant residual disease

Characteristics	N (%)
Age	
Median (Interquartile Range)	55(44.5-65.5)
Menopausal status	
Premenopausal	16 (39)
Postmenopausal	25 (61)
Tumor histology	
Ductal	39 (95.1)
Lobular	1 (2.4)
Other	1 (2.4)
Tumor size at diagnosis	
≤2cm	2 (4.8)
2.1-5cm	16 (39)
≥5.1cm	23 (56.1)
Prior t	
T2	11 (26.8)
T3	14 (34.1)
T4b	15 (36.6)
T4c	1 (2.4)
Histological grade	
1	1 (2.4)
2	10 (24.4)
3	30 (76.2)
Ki67, Median (Interquartile Range)	60 (40-80)
Focality	
Unifocal	38 (92.7)
Multifocal	2 (4.9)
Multicentric	1 (2.4)
Lymph node involvement	
No	9 (31)
Yes	32 (78)
Neoadjuvant received	
Anthracyclics + Taxanes	36 (87.8)
Taxanes	1 (2.4)
Docetaxel + cyclophosphamide	1 (2.4)
Taxanes and platinum	3 (7.3)
Surgery on breast	
Conservative surgery	13 (31.7)
Mastectomy	28 (68.2)
Axillary surgery performed	
BGC	7 (17.1)
BGC + VA	1 (2.1)
GOES	27 (65.9)
Without axillary surgery	6 (14.6)
Adjuvant radiotherapy	40 (97.6)

T; tumor size (TNM), BGC; sentinel lymph node biopsy, VA; axillary emptying.

Table 2. Response to neoadjuvant chemotherapy in patients with triple-negative breast cancer with post-neoadjuvant residual disease

Characteristics	N (%)
RCB	
1	8 (19.5)
2	20 (48.8)
3	13 (31.7)
Residual tumor size (mm)	
Median (Interquartile Range)	23 (10-36)
ypt	
ypT0	1 (2,4)
ypT1a-ypT4c	40 (97.6)
Positive lymph nodes	
0	23 (56.1)
1-3	12 (29.3)
≥4	6 (16.6)
Nodal metastasis size (mm), median (IQR)	2.63 (0-3)
Tumor bed size (mm), median (IQR)	23 (11.50-38.50)
Postneoadjuvant cellularity (%), median (IQR)	50 (12.50-65)
Residual DCIS (%), median (IQR)	1 (0-20)
Progression	
No	30 (76.2)
Yes	11 (26.8)
Progression site	
Regional	2 (18.1)
Loco-regional	2 (18.1)
Distance	7 (63.6)
Remote progression site	
CNS	1 (2,4)
Lungs	2 (4.9)
Ganglion	2 (4.9)
Bones	2 (4.9)
Death	
No	37 (90.2)
Yes	4 (9.8)

RCB: Residual Cancer Burden; ypT: postneoadjuvant residual tumor size; DCIS: ductal carcinoma *in situ*; CNS: central nervous system

3.3. Progression-Free Survival

Median PFS was 25.03 months (95% CI, 13.37 – 36.68), see Figure 1. Eleven patients (26.8%) presented disease progression after starting adjuvant treatment with Capecitabine. Among the total of patients who presented progression, distant progression was documented in seven patients (63.6%), regional progression in 2 (18.1%), and loco-regional progression in 2 (18.1%), as described in Table 2. The most frequent distant progression was lymph node progression in 2 patients (2.9%), followed by metastasis to the lung and bones, both groups with the same representation of 2 patients (4.9%). Among the patients with progression, four died from this cause. When performing the multivariate analysis (Table 3), the statistically significant characteristics associated with patients who received adjuvant Capecitabine were postmenopausal status as a protective factor for progression (HR0.32, 95% CI 0.09 -0.98, p 0.045), and a larger previous size presented a greater risk of disease progression over time (HR1.69, 95% CI, 1.02-2.81, p =0.041).

Figure 1. Progression-free survival in triple-negative breast cancer patients with postneoadjuvant residual disease who received adjuvant Capecitabine

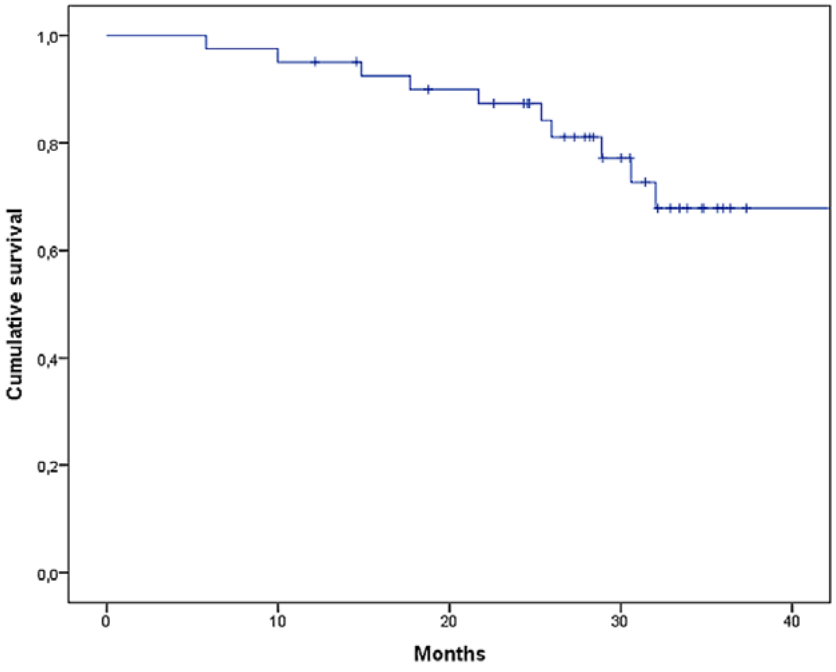


Table 3. Factors associated with time to progression in patients treated with Capecitabine

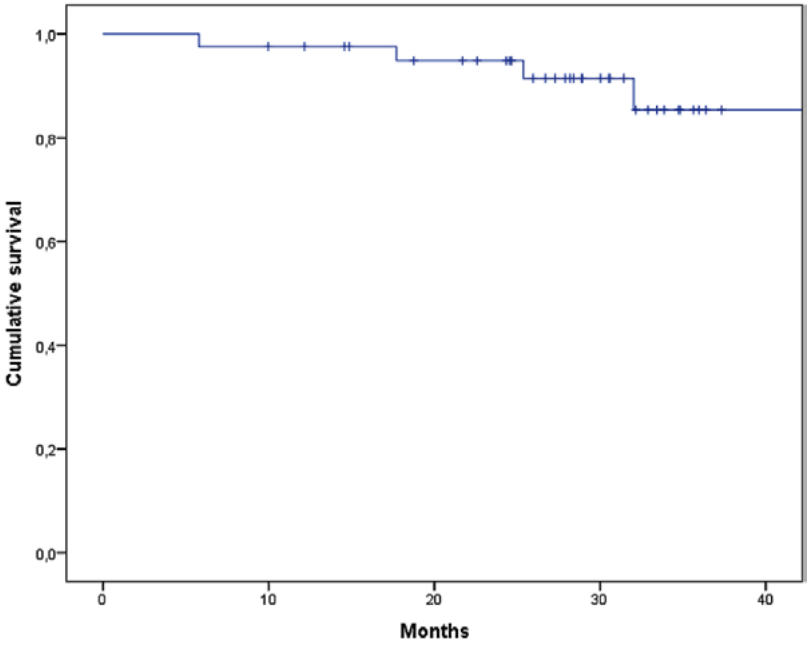
Variable	Univariate		Multivariate	
	RH 95%(CI)	p value	RH 95%(CI)	p value
Age	0.97 (0.93-1.01)	0.162		
Menopause	0.32 (0.09-0.98)	0.045		
Ki67	0.98 (0.95-1.01)	0.347		
Prior t	1.69 (1.02-2.81)	0.041	1.69 (1.02-2.81)	0.041
Previous lymph node involvement	3.02 (0.38-23.94)	0.294		
Breast surgery (mastectomy/conservative)	0.77 (0.23-2.56)	0.681		
Affected lymph nodes				
0	ref	0.039		
1 to 3	1.63 (0.36-7.38			
4	3.85 (1.10-13.39)			
Size of the largest lymph node	1.04 (0.98-1.12)	0.158		
RCB				
1	ref			
2	0.47 (0.06-3.42)	0.208		
3	1.95 (0.39-9.72)			
Focality				
Multifocal or multicentric/unifocal	0.04 (0.01-9.70)	0.854		
NACT				
(Taxanes + platinum /Anthracyclines + taxanes)	2.76 (0.71-10.61)	0.139		
YpT (ypT1a-ypT4c/Yp0)	2.13 (0.62-7.28)	0.228		

T; tumor size, BCR; Residual Cancer Burden, ypT; postneoadjuvant residual tumor size, NACT; neoadjuvant chemotherapy,

3.4. Overall survival

The mean OS was 50.37 months (95% CI, 45.3-55.5) (Figure 2). When performing the survival analysis by RCB, it was found that the mean OS was 51, 50, and 46 months for RCB 1, RCB 2, and RCB 3, respectively; this difference was not statistically significant (p = 0.614). according to the different neoadjuvant schemes or the type of surgery performed.

Figure 2. Overall survival in triple-negative breast cancer patients with postneoadjuvant residual disease who received adjuvant Capecitabine



4. Discussion

In Colombia, there is no clear characterization —retrospective or prospective— of patients with post-neoadjuvant residual disease that evaluates the possible effect of Capecitabine on the OS of the affected people. Therefore, this protocol aimed to objectively and retrospectively evaluate the characteristics of this group of patients and their behavior regarding PFS and OS. Forty-one patients were analyzed, of which 26% presented disease progression at 36 months and, out of them, four died from this cause.

The patients in this study had a median age of 55 years (IQR 44.5-65.6), similar to the Create -82 years of the patients of GEICAM/2003-11_CIBOMA/2004-01 (14). When comparing our results with those studies mentioned above, we observed that the overall survival in them was 94% at 5 years in the group that received Capecitabine (13), which is higher when compared with our study, with an OS of 80.6% at 3 years. In the GEICAM/2003-11_CIBOMA/2004-01 study, the 5-year OS in the Capecitabine group was 86.2% (13), although these results are lower. Therefore, in future prospective studies in our population, it will be necessary to evaluate what unfavorable characteristics are present. One of these characteristics could be that in our study 35.5% were tumors that affected the skin and/or chest wall, in the Create 11 CIBOMA/2004-01 no specification of that characteristic is made. Regarding tumor size, 56.1% had tumors larger than 5 cm, while in Create, in the multivariate analysis, which indicates that our cohort represents a group of patients with more aggressive initial characteristics, and therefore their prognosis would be less favorable despite the use of adjuvant Capecitabine.

In our study, 54.5% of the patients who presented progression were premenopausal. This variable was not evaluated in Create (95% CI, 0.639 - 1.176).

One of the focuses of the study was to evaluate the impact of RCB in terms of prognosis; however, we did not find statistically significant differences in both PFS and OS among groups RCB 1, RCB 2, and RCB 3. When performing the survival analysis by RCB, it was found that the mean survival was 51, 50, and 46 months for RCB 1, RCB 2, and RCB 3, respectively, and this was not statistically significant p 0.614. The Create X and GEICAM/2003-11_CIBOMA/2004-01 studies did not evaluate these variables.

In the meta-analysis carried out by Yan Li and collaborators in 2019, the efficacy of Capecitabine as adjuvant chemotherapy for early-stage TNBC treated with taxane/anthracycline-based chemotherapy was evaluated. They found a significant increase in DFS with the addition of Capecitabine (hazard ratio [HR] = 0.77, 95% CI: 0.66-0.90); a significant improvement in DFS was observed in trials involving six to eight cycles of Capecitabine addition. Furthermore, in a meta-analysis of six trials, a significant increase in overall survival was detected in the Capecitabine group (HR=0.69, 95% CI: 0.56-0.85) (17).

In the neoadjuvant treatment of TNBC, anthracyclines such as doxorubicin and epirubicin are used in dense doses in combination with cyclophosphamide. This approach, known as dose-dense chemotherapy, involves giving anthracyclines at shorter intervals than usual, for instance, every two weeks instead of every three weeks. Dose-dense chemotherapy has been shown to improve pathologic complete response rates, increase disease-free survival, and overall survival compared with standard chemotherapy in some studies (18-22). However, in our study only 22% of patients received this regimen due to barriers to access. Additionally, dose-dense chemotherapy may also be associated with a higher risk of side effects such as febrile neutropenia, which requires support with granulocytic colony factors to reduce this risk of complications (18-21).

The use of immunotherapy, and especially pembrolizumab, has been explored in the neo- and adjuvant management of triple-negative breast cancer (23). The KEYNOTE-522 study evaluated the safety and efficacy of pembrolizumab in combination with neoadjuvant chemotherapy followed by pembrolizumab as adjuvant therapy in patients with early-stage TNBC (24-25). The study included 1174 treatment-naïve patients with stage II or III TNBC and were randomly assigned to receive neoadjuvant chemotherapy with carboplatin/paclitaxel and anthracyclines with or without pembrolizumab. After surgery, patients received pembrolizumab or placebo as complementary adjuvant therapy for one year. The study showed that the addition of pembrolizumab to neoadjuvant chemotherapy increased the overall pCR rate from 51 to 65 percent independent of PD-L1 expression (24-25).

At follow-up, the addition of pembrolizumab improved 36-month DFS (85% with pembrolizumab versus 77% with placebo), with a 37% reduction in events (HR 0.63, 95% CI 0.48-0 ,82) (25). DFS with the addition of pembrolizumab had a greater absolute benefit in patients who did not achieve pCR with NACT than in patients who achieved pCR (94 versus 92 percent), thus raising the need for additional adjuvant therapy in patients with post-neoadjuvant residual disease. Capecitabine can potentially be combined with pembrolizumab in this subgroup; however, the study did not contemplate the addition of Capecitabine in these cases and we still need to wait for mature results from this long-term study in this regard. In our country, treatment with immunotherapy (pembrolizumab) is not available for use in this indication.

This study was observational, with the inherent limitations of this type of design. Results of this study enabled a comparison with international publications about the population characteristics and the benefit of treatment with Capecitabine in this group of patients. However, we found that in this group, in which OS and PFS were analyzed, results were similar to international studies. An important limitation was not having a control group to which Capecitabine was not prescribed as neoadjuvant chemotherapy.

5. Conclusions

Favorable results were observed in patients with triple-negative breast cancer with post-neoadjuvant residual disease with adjuvant Capecitabine, particularly in postmenopausal patients with smaller previous size, regardless of the RCB, since they presented better PFS and OS. More studies are needed to make a comparison between patients who received adjuvant Capecitabine and others who did not receive another regimen.

6. Abbreviations

OS: Overall Survival

PFS: Progression-free survival

RCB: residual cancer burden

TNBC: triple negative breast cancer

HR: Hazard ratio

7. Administrative information

7.1. Acknowledgment

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7.2. Authors' contribution

Arnon J. Oviedo-Tábora: Conceptualization, validation, visualization, methodology, project management, writing: review and editing. **Elsa Maria Vásquez Trespalacios:** Conceptualization, validation, visualization, methodology, project management, writing: review and editing. **Fernanda Ximena Bravo:** Conceptualization, validation, visualization, methodology, project management, writing: review and editing. **Javier Mauricio Cuello López:** Conceptualization, validation, visualization, methodology, project management, writing: review and editing. All authors read and approved the final version of the manuscript.

7.3. Financing

The study was financed with each researcher's own resources.

7.4. Statements

The protocol of this study was approved by the institutional committee of ethics of research in human beings of the CES University (cod Acta2 Ae-973) and the Fundación Colombiana de Cancerología Clínica Vida. Since this is a retrospective study without any intervention in the care of patients, consent was not required. Patient data were guaranteed to be submitted anonymously and confidentially.

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