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Mini Review

Polymers in Clinical Trials for Cancer Therapeutics

Preeya D Katti*

American University of the Caribbean, Sint Maarten

ISSN: 2770-6613

***Corresponding authors:** Preeya D Katti, American University of the Caribbean, Sint Maarten
Email: preeya.katti@gmail.com

Submission: July 07, 2024
Published: July 24, 2024

Volume 5 - Issue 5

How to cite this article: Preeya D Katti*. Polymers in Clinical Trials for Cancer Therapeutics. Polymer Sci peer Rev J. 5(5). PSPRJ. 000621 2024.
DOI: 10.31031/PSPRJ.2024.05.000621

Abstract

Polymers are extensively used in medicine as components of several biomedical devices, as implants for restoring functions of tissues, and as delivery agents of therapeutics. Recent advances in the ability to tailor mechanical properties, degradation behavior, and the bioactivities of polymers have greatly benefitted research advances in the biomedical engineering field, resulting in many publications. The long time needed for federal approvals of the devices and the inherent series of biological *in vivo* experiments that are required prior to clinical trials, have greatly limited the use of polymers for drug delivery in devices or technologies investigated under clinical trials for cancer therapeutics. This brief review elucidates the clinical trials worldwide that utilize polymers for therapeutics for various cancers.

Keywords: Cancer therapeutics; Polymer drug delivery; Degradable polymers; Clinical trials

Introduction

As per the World Health Organization, Cancer remains the leading cause of death worldwide, resulting in about 10 million deaths in 2020. Worldwide, nearly one in six deaths are attributed to cancer. Further, it is estimated that there will be over 35 million new cancer cases in 2050. To address the increasing cancer burden, the World Health Assembly passed a new resolution, "Resolution Cancer Prevention and Control," in an attempt to reduce the increasing mortality due to cancer worldwide [1]. Besides enabling medical access and increasing political commitments, this resolution also seeks to enhance basic research on human cancer. Novel polymeric materials for the delivery of new therapeutics remain one of the foremost areas of research owing to the advances in polymer sciences enabling accurate tuning of structure and properties of the polymers. Due to the properties of biocompatibility and controlled degradation within the bodily environment, polymers are extensively used in clinical medicine to treat, diagnose, and evaluate many diseases [2-4]. Specifically, the last two decades have shown immense advancements and studies using polymeric nanoparticles as delivery agents in cancer therapeutics [5-10]. Yet the use of polymers for drug delivery in devices or technologies investigated under clinical trials for cancer therapeutics remains limited. The majority of the ongoing clinical trials are interventional, with only a few observational trials aiming to reduce the cancer burden. Controlled polymer degradation is one of the primaries deciding factors for the use of polymers in biomedical applications.

Polymer degradation results from various conditions that alter a polymer's physical properties. The key factors that are responsible for polymer degradation are,

a. Thermal changes, such as the effect of elevated temperatures, cause damage to the polymer chains.

b. Exposure to UV light can cause photo-oxidation of the polymer, resulting in chain scission.

c. Oxidative stress can result when the polymeric chains are exposed to oxygen, causing damage to the polymeric chains.

d. Hydrolysis occurs when a reaction with water causes polymeric chains to break down.

e. Mechanical stresses, such as shear stresses can break down polymeric chains

f. Radiative damage can occur, causing crosslinking or chain scission, such as when exposed to gamma rays.

Of the above six types of degradation, the bodily fluids and the body environment are conducive to degradation due to hydrolysis, oxidative stress, and, occasionally, mechanical stresses. The extent of hydrolysable functional groups affects the degradation behavior of polymers. The common hydrolysable functional groups include amides, esters, lactones, and urethanes. As a result, the biomedical industry has formulated many biocompatible polymers with controlled degradation through structural variations and placement of the functional groups. Many biodegradable polymers have shown extensive applications in the biomedical industry for cancer drug delivery due to their tunability, degradation characteristics, and biocompatibility with various human cells [11-13]. Hundreds of polymeric structures are investigated for biomedical applications, yet only a handful are elevated to be used in clinical trials for drug delivery systems for cancer. Table 1 shows the polymeric materials that are used in clinical trials for cancer therapeutics.

Table 1: List of polymeric materials used in clinical trials (Data obtained from Clinical Trials.gov).

NCT Number	Study Title	Study Status	Health Conditions	Sponsor	Location	Material
NCT03774680	Targeted Polymeric Nanoparticles Loaded With Cetuximab and Decorated With Somatostatin Analogue to Colon Cancer	UNKNOWN	Colon Cancer, Colorectal Cancer	Ahmed A. H. Abdellatif	Assiut, Egypt	ethylcellulose
NCT00629499	Nanoparticle Albumin-Bound (Nab) Paclitaxel/ Cyclophosphamide in Early-Stage Breast Cancer	COMPLETED	Breast Cancer	SCRI Development Innovations, LLC	Nashville, TN	albumin
NCT00736619	Weekly Nanoparticle Albumin-Bound Paclitaxel (Abraxane) + Weekly Cetuximab + Radiation Therapy (IMRT, Intensity-Modulated Radiation Therapy) in Patients With Stage III-IVB Head and Neck Squamous Cell Carcinoma (HNSCC)	COMPLETED	HEAD & NECK Cancer	Memorial Sloan Kettering Cancer Center	NY, NY	albumin
NCT05200650	A Single Arm, Prospective, Open Label, Multi-Center, Phase Ib Study to Evaluate the Safety, Tolerability and Initial Efficacy of a Single Intra-tumoral Injection of IntraGel's Polymer-based Cisplatin-loaded Gel (TumoCure) in Subjects With Progressive or Radio-resistant Primary Head and Neck Tumor	RECRUITING	Head and Neck Cancer	IntraGel Therapeutics	Nazareth, Israel	proprietary degradable polymer
NCT05456022	Therapeutic Efficacy of Quercetin Versus Its Encapsulated Nanoparticle on Tongue Squamous Cell Carcinoma Cell Line	UNKNOWN	Oral Cancer	Cairo University	Cairo, Egypt	PLGA-PEG
NCT06199895	Clinical Efficacy and Safety of Paclitaxel Polymeric Micelles for Injection in the Treatment of Patients With Taxans-resistant Pancreatic Adenocarcinoma, Cholangiocarcinoma, Lung Cancer, Gastric Cancer, Esophageal Carcinoma, or Breast Cancer	RECRUITING	Pancreatic Adenocarcinoma, Cholangiocarcinoma, Lung Cancer, Stomach Cancer, Esophageal Carcinoma, Breast Cancer	Liu Huang	Wuhan, China	Micelles

NCT03585673	Docetaxel-polymeric Micelles(PM) and Oxaliplatin for Esophageal Carcinoma	UNKNOWN	Esophagus Squamous Cell Carcinoma (SCC), Metastatic Cancer	Sung Yong Oh	Busan, Korea	Micelles
NCT00886717	Paclitaxel-Loaded Polymeric Micelle and Carboplatin as First-Line Therapy in Treating Patients With Advanced Ovarian Cancer	TERMINATED	Ovarian Cancer	Asan Medical Center	Seoul, Korea	Micelles
NCT06356688	A Clinical Study on the Efficacy and Safety of Paclitaxel Polymer Micelles and Cisplatin Combined With Cadonilimab as a Neoadjuvant Therapy for Locally Advanced Esophageal Squamous Cell Carcinoma	NOT_YET_ RECRUITING	Locally Advanced Esophageal Squamous Cell Carcinoma, Neoadjuvant Therapy	Sun Jing	Nanjing, China	Micelles
NCT01116635	Clinical Study Examining the Safety and Efficacy of Doxorubicin Drug Eluting Microspheres Transarterial Embolization in the Setting of Hepatocellular Carcinoma (HCC)	COMPLETED	Hepatocellular Carcinoma	University of British Columbia	BC, Canada	Micelles
NCT04783831	Biodegradable Pancreatic Stents for the Prevention of Postoperative Pancreatic Fistula After Cephalic Pancreaticoduodenectomy	UNKNOWN	Pancreatic Fistula, Pancreas Neoplasm, Stent Disintegration, Pancreatic Cancer, Pancreatic Anastomotic Leak	Hospital Universitario Virgen de la Arrixaca	Murcia, Spain	poly p-dioxanone, trimethylene carbonate, and glycolide.
NCT04619056	First-in-man Clinical Trial of CEB-01 PLGA Membrane in Recurrent or Locally Advanced Retroperitoneal Soft Tissue Sarcoma	ACTIVE	Locally Advanced Soft Tissue Sarcoma, Recurrent Soft Tissue Sarcoma	CEBIOTEX	Barcelona, Madrid, Valencia, Cataluña,	A proprietary biocompatible polymeric PLGA nanofiber membrane (CEB-01) containing the active substance 7-ethyl-10-hydroxycamptothecin developed by CEBIOTEX
NCT04803019	Transarterial Embolization Alone Versus Drug-Eluting Beads Chemoembolization for Hepatocellular Carcinoma (RAD-18-TAcE)	UNKNOWN	Carcinoma, Hepatocellular	IRCCS Azienda Ospedaliero-Universitaria di Bologna	Bologna, Italy	Proprietary microsphere beads are used. Typically, these are made of well calibrated, biocompatible, nonresorbable hydrogel materials. Bead microspheres consist of a polyvinyl alcohol or sodium poly(methacrylate) hydrogel and an outer biocompatible shell of poly(bis[trifluoroethoxy] phosphazene).
NCT01116635	Clinical Study Examining the Safety and Efficacy of Doxorubicin Drug Eluting Microspheres Transarterial Embolization in the Setting of Hepatocellular Carcinoma (HCC)	COMPLETED	Hepatocellular Carcinoma	University of British Columbia	BC, Canada	Superabsorbant polymeric microspheres are used in this clinical trial. Often these microspheres consist of sodium acrylate and vinyl alcohol copolymer.

As seen in (Table 1), several biodegradable polymers are extensively utilized in drug delivery and are being investigated in clinical trials. These include ethyl cellulose, albumin, and other degradable polymers, such as polylactic acid and polyglycolic acid, as well as their copolymers. Another widely used structure involves self-assembling amphiphilic polymers with hydrophilic and hydrophobic units, resulting in polymeric micelles [14]. Engineered hydrophobic cores and hydrophilic shells of the polymeric micelles enable great design adaptability for the delivery of various therapeutics. The excellent biocompatibility, pharmacokinetics, adhesion to bio surfaces, targetability, and durability of the polymeric micelles and their engineered structures make them beneficial polymeric systems for biomedical applications. Polymeric micelles are extensively used in various clinical trials worldwide. Although most studies do not clarify specific polymeric micelles, the polymeric micelles are often Pluronic P123, an amphiphilic block copolymer, or Methoxy poly(ethylene glycol)-conjugated linoleic acid. Pluronic P123 is a symmetric triblock copolymer comprising Poly(Ethylene Oxide) (PEO) and Poly(Propylene Oxide) (PPO) in an alternating linear fashion, PEO-PPO-PEO.

Besides the delivery of drugs through controlled degradation of the polymeric delivery agent, other applications in cancer therapeutics involve embolization therapy for treating liver cancer with degradable microspheres [15]. Many commercially available microspheres that are made up of Poly(Methylacrylic Acid) coated with Polyzene-F, copolymer of PEG and Diacrylamide, Starch, Gelatin, Collagen-coated PLGA, Tris-Acryl Gelatin, PVA, PVA Hydrogel cross-linked with acrylic Polymer, Acrylamido sulfonate-PVA Hydrogel, Poly(Methylacrylic Acid) coated with Polyzene-F, copolymer of PEG and Diacrylamide, Starch, Gelatin, collagen-coated PLGA, Triiodobenzyl-Modified Acrylic Polymer, Triiodobenzyl-Modified Acrylamido-sulfonate PVA Hydrogels. As shown in Table 1, polymer beads made of hydrogel cores of polyvinyl alcohol are also used. One important application is in a clinical trial involving the use of drug eluting beads in combination with the Trans Arterial Chemoembolization (TACE) treatment for liver cancer. Proprietary microsphere beads are used. Typically, these are made of well calibrated, biocompatible, non-resorbable hydrogel materials. The beads are often produced from highly absorbent polymers such as polyvinyl alcohol. Bead microspheres consist of a polyvinyl alcohol or sodium Poly(Methacrylate hydrogel and an outer biocompatible shell of Poly(Bis[Trifluoroethoxy]Phosphazene) are used. The drug and microsphere are held together by the interaction of the cationic anticancer drugs (doxorubicin) with the anionic functional groups of the microspheres [16]. Superabsorbent polymer microspheres made of sodium acrylate and vinyl alcohol copolymer are a useful eluting agent attempted in many studies [17]. PLGA used as nanofiber membranes in proprietary structures are being tested for efficacy against Retroperitoneal Soft Tissue Sarcoma. Controlled drug delivery is attempted in tubular stents to prevent Pancreaticojejunal Anastomotic Stricture [18].

Conclusion

Although a large number of polymers are investigated for applications in cancer drug delivery systems, only a few are attempted for clinical trials worldwide. The extensive time and costs associated with animal models and other *in vivo* experiments needed by various federal agencies worldwide further diminishes the application of viable polymeric systems to clinical trials. There is a great need to screen therapeutics easily and at a low cost without using *in vivo* systems. Many new drug formulations are hence being evaluated as new anticancer drugs on *in vitro* models [19-23] that attempt to recapitulate the *in vivo* systems. The use of robust 3D *in vitro* models, often called testbeds, is showing increased prevalence in the literature [24], and more viable polymeric systems are likely to be used in cancer therapeutics in the future due to the reduced time and expense of testbeds compared to animal model experiments. The testbeds are likely to be used as screening tools to reduce the trials through animal models and speed up the bench-to-bedside applications of polymers.

Acknowledgment

The author acknowledges support from her academic institution.

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