

# FUZZY PROMETHEE ANALYSIS OF LEUKEMIA TREATMENT TECHNIQUES

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**Abstract – Objective:** Leukemia is an abnormal division of cells that results in the formation of abnormal white-blood cells. Therapy is very important in order to increase the chances of survival from the disease. The objective of this research is to analyze the most common therapeutic techniques for leukemia, such as radiotherapy, targeted drug treatment, immunotherapy, gene-therapy, stem-cell transplant, and chemotherapy to determine the most suitable treatment option using the Fuzzy Preference Ranking Organization Method for Enrichment of Evaluations (PROMETHEE), which is a decision-making tool.

**Materials and Methods:** Fuzzy PROMETHEE deals with problems characterized by uncertainty and is based on a comparison of the alternatives with regard to their criteria. Computing the differences in the alternatives, contribution is based on the weight and preference function of each criterion. The criteria selected in this study include cost of treatment, cost per session, period of treatment, time per session, survival rate, side effects and advantages. After defining the values of each criteria and assigning weights, decision lab software was used to obtain the complete ranking.

**Results:** The evaluation results showed that radiation therapy outclasses other treatment techniques in leukemia therapy based on the selected criteria, importance, and weights of the parameters, followed by targeted drug therapy, immunotherapy, stem cell transplant and finally, chemotherapy.

**Conclusions:** Having applied fuzzy PROMETHEE in the analysis of the different treatment techniques for leukemia, we were able to achieve reliable results that can aid physicians and patients to embark on a favorable treatment option.

**KEYWORDS:** Leukemia, Therapeutic techniques, Fuzzy PROMETHEE, Decision-making.

## INTRODUCTION

Leukemia is an abnormal growth of cells in the bone marrow and white-blood cells. Although leukemia is more prevalent in adults, it is the most common type of cancer in children less than 15 years of age<sup>1</sup>. Between 2010 and 2014, leukemia was rated as the sixth leading cause of cancer deaths worldwide, and about 22,840 people are expected to die from the disease in 2019 in the United States of America only, with 61,780 new diagnosed cases<sup>2</sup>. Depending

on the cancer level and type, treatments like stem-cell transplant, immunotherapy, targeted drug therapy, and radiation therapy are explored. With current advancements in treatment techniques, genes can be used as a medicine (gene therapy), acting in different approaches to fix the defective genes.

It is often very difficult to obtain crisp data that accurately capture a problem and to conduct analysis using that data that will ultimately result in an optimal solution. Fuzzy Preference Ranking Organization Methods for Enrichment of Evaluations



(PROMETHEE) is a technique that combines the concept of fuzzy logic and that of the PROMETHEE method. Fuzzy logic provides the user with the opportunity to define the problem using vague but realistic parameters and then transform the linguistic variables to mathematical variables. Using PROMETHEE, the decision maker can compare different fuzzy values. In the study conducted by Uzun Ozsahin et al<sup>3</sup>, different nuclear medicine imaging devices were compared using fuzzy PROMETHEE and a detailed explanation of the fuzzy PROMETHEE technique was given. Goumas et al<sup>4</sup> ranked the energy exploitation schemes of a low temperature geothermal field using fuzzy PROMETHEE. Ozgen et al<sup>5</sup> proposed a method that combined the modified DELPHI method, AHP (Analytical Hierarchy Process) and PROMETHEE for curbing the difficulties experienced in the selection process of appropriate tools and machines that affect a manufacturing operation's effectiveness. Analysis of breast cancer treatment techniques<sup>6</sup>, an evaluation of X-ray based medical imaging devices<sup>7</sup>, effective analysis of image reconstruction algorithms in nuclear medicine<sup>8</sup>, and evaluation of lung cancer treatment techniques<sup>9</sup> using fuzzy PROMETHEE, are some examples of research that has been completed.

In this paper, we present different therapeutic techniques for the treatment of leukemia and then analyze them using the fuzzy PROMETHEE method with respect to certain factors that affect the quality of treatment, such as cost of treatment, cost required for a single session of the specific treatment mode, time needed for full procedure and session, survival rate of the subject after taking the treatment, side effects that can arise post-treatment, and the advantages and disadvantages of each treatment in order to determine the most suitable treatment technique to embark on.

## MATERIALS AND METHODS

### LEUKEMIA TREATMENT TECHNIQUES: CHEMOTHERAPY

Chemotherapy is the use of drugs in an attempt to eliminate cancerous cells. It is the most frequently applied remedy to treat leukemia. It is a treatment used to shrink and slow the abnormal division of the leukemic cells. Chemotherapy is a treatment embarked upon to either shrink large cells before a more definitive treatment procedure is implemented to eliminate the cells or as a secondary treatment option to completely eliminate carrying cells from a previous treatment. Chemotherapy is administered orally, intravenously, or through targeted drug delivery to the nervous system to minimize the discomfort of multiple needles. Chemotherapy may sometimes affect normal cells, resulting in some manageable

side effects such as illness in the digestive system, stomach problems, heart muscle problems, weakness, pain and numbness of the nervous system, problem in sexual activities and reduced blood cell count.

### RADIATION THERAPY

Radiotherapy is the use of high dose radiation to destroy cancerous cells and shrink the tumors. The application of high dose radiation does not instantly destroy the cells but rather inhibits the abnormal division of the cancerous cells.

There are two principal types of radiation therapy: external beam radiation therapy (EBRT) and brachytherapy (internal radiation therapy). In external beam radiation therapy, an external radiation source is focused on the cancerous cells. Brachytherapy uses radioactive substances encapsulated in delivery systems such as catheters, which are placed close to or directly on the cancerous cells<sup>10</sup>.

Radiotherapy is usually used as a combination treatment together with either chemotherapy or immunotherapy in order to maximize the effect of the treatment. Radiation therapy not only affects the cancerous cells, but one of its drawbacks is that can also affect cells, especially in the case of EBRT.

### STEM-CELL TRANSPLANT

Stem cells are origin cells that have the ability to differentiate and produce cells of the same kind or another kind. The transplant of these origin cells is a good remedy for replacing mother differentiating cells that are involved in abnormal division or cells that have been destroyed by radiotherapy or chemotherapy.

The source of these cells can be autologous (from the patient) or allogenic (from another person with similar genes). However, an autologous source is preferred because it eliminates the risk of an immune response from the body. Transplantation of the cells is done through a catheter delivered into the blood stream from where they travel to the bone marrow. The procedure is similar to receiving a blood transfusion. The side effects of stem-cell transplantation include digestive problems, lung problems and blockage of blood in the liver.

### TARGETED THERAPY

Targeted drug therapy is a technique that uses drugs to target the cancerous cells, inhibiting their growth and eventually destroying them if possible. Unlike in chemotherapy that also affects healthy cells, this technique only targets cancerous cells and minimizes the effects on healthy cells. The design of the drugs being used in the targeted therapy is critically tailored to engulf the abnormal cells without interfering with the normal cells. The drugs for targeted therapy are administered either orally or intravenously, and the drugs are tailored with antibodies that interact with

the genes or proteins of the cancerous cells to inhibit their growth. The side effects of targeted drug therapy include blood clumping and skin-related issues. Nevertheless, targeted drug delivery is less toxic for healthy cells than chemotherapy.

### IMMUNOTHERAPY

This mode of treatment uses the human defensive mechanism to boost the body's immune response. The drugs used for immunotherapy are specifically designed from substances from the body's immune system in order to slow or stop the growth and division of cancerous cells, boost the body's immune system to destroy cells and slow or stop the spread of the cancerous cells to other parts of the body. Administration of immunotherapy drugs for leukemia treatment is done either orally or intravenously. The side effects of immunotherapy include body pains, swelling and soreness with flu-like symptoms.

### APPLICATION OF FUZZY PROMETHEE

The concept of fuzzy PROMETHEE is based on the fusion of fuzzy logic and PROMETHEE. Fuzzy logic can be defined as a class of multi-valued logic that permits intermediate values in the form of multi-valued logic, in which the truth-values of the variables may be any number between 0 and 1 (i.e., the truth values are obtained in degrees ranging between completely true to completely false). Fuzzy logic systems are applied to design processes to enhance efficiency and simplicity. PROMETHEE was developed by<sup>11,12</sup>. It is a multi-criteria decision-making (MCDM) technique that mutually compares related alternatives with regard to their related and selected criteria. PROMETHEE is advantageous compared to other MCDM techniques due to its efficiency and ease of application. The PROMETHEE method requires only two types of information: information on the weights of the criteria considered and the decision-maker's preference function when comparing the contribution of the alternatives in terms of each separate criteria<sup>13</sup>. A detailed explanation of the fuzzy PROMETHEE technique can be found in<sup>14</sup>.

The importance of the parameters on a linguistic scale using a triangular fuzzy scale is shown in Table 1. The triangular fuzzy scale, proposed by Yager<sup>15</sup> in 1981, was determined by the center of weights of the surface of its membership function. The membership function can be given as shown in Equation 1:

$$\mu_{\tilde{F}}(x) = \begin{cases} \frac{x-a}{n-a}, & a < x \leq n \\ \frac{b-x}{b-n}, & n < x < b \\ 0, & \text{otherwise} \end{cases}$$

The decision for the weights of these parameters was made based on a specialist's opinion on an aver-

age patient; these weights can be changed based on individual patients, the stage of the cancer and other factors that could affect the results of the analyses. Furthermore, more parameters can be added based on the preferences of the decision maker and the situation. To defuzzify the triangular fuzzy numbers to crisp values and obtain the weight for each criteria, the Yager index<sup>15</sup> was applied by using Equation 2:

$$(3N - a + b)/3$$

We used the Gaussian preference function on the visual PROMETHEE decision lab program to analyze each criterion. Table 2 shows the criteria and corresponding values gathered after an extensive literature review. The preferences and defuzzified triangular numbers are shown in Table 3.

## RESULTS

Radiotherapy emerged as the most preferred treatment technique for leukemia compared to other treatment techniques with a favorable cost of treatment, cost per session, period of treatment, time per session and survival rate, albeit with a negative rating for side effects and advantages. Targeted drug therapy, on the other hand, emerged as the least favorable treatment option, with its only favorable points being very high advantages and low side effects in comparison to the other techniques. Table 4 shows the ranking of the techniques with the positive and negative outranking flows as well as the net flow. Figure 1 is a rainbow view of the evaluation results, indicating the strong and weak points of each technique.

## DISCUSSION

This novel study has successfully compared alternative therapy techniques used in leukemia treatment. This provides numerical information to decision makers, which could be the clinicians, the patients and their families, on the advantages and disadvantages of the treatment options. To our knowledge, there is no previous research that can be compared with our results in regard to the improvement in decision-making via PROMETHEE. In fact, the only traditional method is where the clinician performs a preoperative assessment by reviewing the patient medical history and overall physical performance and selects the most appropriate therapy technique based on experience. Future research should focus on personalizing this analysis on individual patients, where numerical information is provided by using the patient's physical conditions, stage of cancer, medical history etc.

Treatment of leukemia is important for the survival of patients affected with this abnormal growth of cells. A significant important factor is treatment



**TABLE 1.** Linguistic scale with corresponding triangular fuzzy scale and weight assignment.

Linguistic scale for evaluation	Triangular fuzzyscale	Importance ratings of criteria
Very High (VH)	(0.75, 1, 1)	Survival rate
High (H)	(0.50, 0.75, 1)	Cost of treatment, cost per session
Medium (M)	(0.25, 0.50, 0.75)	Period of treatment, time per session
Low (L)	(0, 0.25, 0.50)	Side effects, advantages
Very Low (VL)	(0, 0, 0.25)	

**TABLE 2.** Criteria and their corresponding values for leukemia treatment alternatives.

Alternatives	Cost of treatment (\$)	Cost per session (\$)	Period of treatment (weeks)	Time per session (min.)	Survival rate (%)	Side effects	Advantages
Radiation Therapy	50,000	5,000	8	15	88.5	Moderate	Moderate
Chemotherapy	120,000	9,000	48	135	65	Low	Very high
Immunotherapy	100,000	5,400	8	80	95	Very low	Very high
Stem Cell Transplant	100,000	N/A	5	150	68	Moderate	Very high
Targeted Drug Therapy	130,000	5,000	7	80	95	Very low	Very high

method embarked upon to ensure that the cancerous cells are completely eradicated and that the patient obtains the maximum results from the treatment and is comfortable during the process.

Fuzzy PROMETHEE affords the decision maker the opportunity to conduct an analysis of different parameters including parameters that do not consist of crisp data as well as the opportunity to perform this analysis with the criteria that are available. PROMETHEE as well as other multi-criteria decision-making techniques are important and useful tools in assisting users with making decisions, and it is important to note that they are currently only used to provide assistance when making analysis to arrive at a decision. An expert opinion is still very important for arriving at an educated decision and the

final results from the analysis should not be followed blindly without obtaining expert opinions, especially in cases that involve the health and lives of patients.

## CONCLUSIONS

With the application fuzzy of PROMETHEE in the analysis of the different treatment techniques for leukemia, we were able to achieve reliable results that can aid physicians and patients to embark on a favorable treatment option. According to the results of this analysis, radiation therapy emerged as the most preferable treatment with a favorable cost of treatment, treatment time, time per session, survival rate and the cost of a session, with the weak points

**TABLE 3.** Selected preferences and assigned weights defuzzified into crisp numbers.

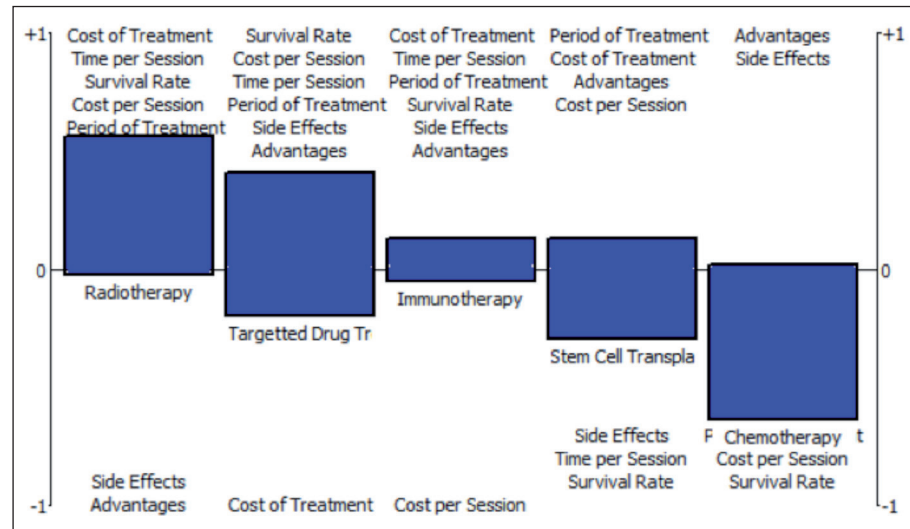
Criteria	Cost of treatment (\$)	Cost per session (\$)	Period of treatment (weeks)	Time per session (min.)	Survival rate (%)	Side effects	Advantages
Max/Min	Minimum	Minimum	Minimum	Minimum	Maximum	Minimum	Maximum
Weight	0.75	0.75	0.50	0.50	0.92	0.25	0.25

**TABLE 4.** Complete ranking of leukemia treatment alternatives

Complete Ranking	Alternatives	Positive outranking flow	Negative outranking flow	Net flow
1	Radiation therapy	0.6140	0.0873	0.5267
2	Chemotherapy	0.4342	0.2296	0.2047
3	Immunotherapy	0.3669	0.2985	0.0684
4	Stem cell transplant	0.1853	0.3586	-0.1734
5	Targeted drug therapy	0.0846	0.7110	-0.6264



**Fig. 1.** Evaluation results with positive and negative sides of the alternatives.



of the treatment technique being the side effects and the advantages. The findings of this study provide decision makers with the opportunity to view the treatment techniques available with the features that make them favorable or not.

Using fuzzy PROMETHEE allows the user to easily modify the parameters by adding more criteria and changing their importance and weights depending on the condition and preference of the patient. Fuzzy PROMETHEE is a very effective method that can be employed in decision-making situations. It gives the user a wide range of control over the parameters and their importance; fuzzy PROMETHEE weighs the parameters against each other to determine the combination of parameters that make an option better than other available options.

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#### CONFLICT OF INTEREST

The authors report no conflict of interest.

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